AN INQUIRY INTO THE IMCLONE CANCER-DRUG STORY

HEARINGS

BEFORE THE

SUBCOMMITTEE ON
OVERSIGHT AND INVESTIGATIONS

OF THE

COMMITTEE ON ENERGY AND
COMMERCE
HOUSE OF REPRESENTATIVES

ONE HUNDRED SEVENTH CONGRESS

SECOND SESSION

JUNE 13 and OCTOBER 10, 2002

Serial No. 107–142

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AN INQUIRY INTO THE IMCLONE CANCER-DRUG STORY

THURSDAY, JUNE 13, 2002

HOUSE OF REPRESENTATIVES,
COMMITTEE ON ENERGY AND COMMERCE,
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS,
Washington, DC.

The subcommittee met, pursuant to notice, at 9 a.m., in room 2123, Rayburn House Office Building, James C. Greenwood (chairman) presiding.

Members present: Representatives Greenwood, Bilirakis, Stearns, Gillmor, Burr, Whitfield, Bass, Fletcher, Tauzin (ex officio), Stupak, DeGette, and Rush.

Staff present: Alan Slobodin, majority counsel; Mark Paoletta, majority counsel; Tom Dilenge, majority counsel; Tony Cooke, majority counsel; Will Carty, legislative clerk; David Nelson, minority investigator and economist; and Jessica McNiece, minority staff assistant.

Mr. GREENWOOD. The subcommittee will come to order. It is the Chair's intention to recess the subcommittee until 10:30 or 20 minutes after the conclusion of the full committee markup, whichever is later. The Chair reminds witnesses who have received a subpoena that they remain subject to the committee's compulsory process. The committee stands in recess until 10:30 a.m. or 20 minutes after the conclusion of the full committee markup, whichever is later.

[Brief recess.]

Mr. GREENWOOD. The meeting will come to order. The Chair recognizes himself for an opening statement.

In the past, when Americans of my generation have thought about the development of life-saving miracle drugs, the images most likely to come to mind have been those of self-effacing men of science, like Alexander Fleming and Jonas Salk. In 1952, when Salk was convinced that he had developed a vaccine for the deadly scourge of polio, he didn't rush out to the marketplace with effusive praise either to the drugs efficacy or its money making possibilities. Instead he vaccinated volunteers, including his wife and three sons. And only when it became clear that even though the volunteers had developed antibodies to the disease, none had become ill, did he finally publish his findings the following year in the Journal of the American Medical Association.

Now flash forward to 2001. Another doctor, this time with a Ph.D. in immunology, claims that his company is bringing another miracle drug to the market. Like Salk in 1952, the disease he is

researching strikes down roughly 60,000 thousand Americans each year. That disease is colorectal cancer. The name of this new drug is Erbitux. And here the similarity comes to a glaring halt.

It appears that, instead of concentrating his focus on the need to carefully conduct clinical trials that the introduction of a breakthrough medicine demands, ImClone seemed more focused on the sales pitch. Dr. Samuel Waksal is quoted as having said that Erbitux was, "going to be the most important new oncology launch ever." Investors and hopeful patients alike were told that the results of ImClone's pivotal clinical trial were, "knock-your-socks-off exciting."

While others who had invested and hoped and perhaps prayed for a cure were busy having their hopes dashed, Dr. Samuel Waksal and others close to him appear to have been too busy cashing out to pay attention to those for whom the success or failure of Erbitux represented the difference between life and death.

Today the subcommittee examines the unraveling of ImClone, whose highly publicized race to develop and market what some thoughtful researchers still consider to be a promising therapy, failed so spectacularly. Presently, only two drugs have established efficacy for treatment of metastatic colorectal cancer. If these drugs are not effective in a particular patient, there is no real therapy available to save that patient.

ImClone sought accelerated approval for Erbitux to meet this unmet medical need of colorectal cancer patients who had failed standard chemotherapy treatments. For these patients with no other options, many believed that Erbitux was their best hope at survival, and late last year they had every reason to count on a speedy FDA approval. These cancer patients and their families were told that Erbitux was a leading monoclonal antibody, part of a new class of targeted therapies, drugs such as Gleevec and Herceptin, that doctors hoped would revolutionize cancer treatment and would not cause the severe side effects of toxic chemotherapy.

They were assured by ImClone that Erbitux was going to be approved in early 2002. They believed in a company that had a number of leading oncologists on its board of directors. They believed in a company that in October 2001 had entered into a much publicized and record setting $2 billion strategic agreement with a leading pharmaceutical maker, Bristol-Myers Squibb, an agreement which included an up-front $1 Billion tender offer for ImClone stock from Bristol to ImClone's existing shareholders at the premium price of $70 a share.

On December 17, 2001, ImClone was one of seven biotechnology companies included for the first time in the NASDAQ 100 index. Excitement and confidence in ImClone were reflected in such media reports as a December 26, 2001 Los Angeles Times story, which proclaimed, in almost giddy language, that "Erbitux, a colon cancer treatment from ImClone Systems Inc., is set to make one of the biggest splashes of 2002."

Yet just days later, the hopes of cancer patients were crushed when they learned that the deficiencies in the Erbitux clinical trials were so severe that FDA took the rare action of issuing a refusal-to-file letter. This meant that, under the 60-day deadline to determine whether a new product licensing application was ade-

quate enough to be evaluated, FDA found such serious deficiencies that the agency could not even continue its review.

After announcing FDA's refusal-to-file letter, ImClone executives told investors and the public that the problem was simply some missing documentation and suggested that it was an easily fixable problem of supplying the missing proof in the pivotal study. But soon thereafter, excerpts of the non-public FDA refusal-to-file letter appeared in a trade publication, revealing the real truth behind the FDA's action: The clinical study problems were much more than a failure to provide some data elements. To bring the drug to market, ImClone would need to conduct additional studies to demonstrate the drug's efficacy as a combination therapy for cancer, which would take substantial amounts of time and could in fact raise more questions about Erbitux than they would answer.

How did a highly touted drug like Erbitux, which attracted the interest of Bristol-Myers Squibb to the tune of $2 billion, stumble so completely before even arriving at the regulatory starting gate? Cancer patients and their families want to know. And this subcommittee chairman wants to know too.

Today, the subcommittee's investigative detailee, accompanied by the committee's scientific consultant, will present the preliminary staff report on this matter. Here are some of the staff's key findings: FDA refused to file ImClone's application not just because of missing documentation and data discrepancies, but also because the pivotal study was neither adequate nor sufficiently well-controlled to meet Federal requirements. Yet, in an August 2000 meeting between ImClone and FDA to discuss this study, ImClone's proposed study design to support accelerated approval was deemed by FDA to be probably acceptable.

FDA's decision to accept the protocol design in effect overruled the initial recommendation of the primary FDA medical reviewer, who argued it failed to meet Federal requirements. Moreover, FDA's decision appears to be based on a significant misunderstanding as to the rigor of the study protocol, a misunderstanding that should have been quite apparent to ImClone from its discussions with FDA, but one ImClone did not seek to correct.

As FDA reviewers examined the study more closely in the context of ImClone's formal licensing application, these protocol design issues finally received the attention they deserved, but by that point it was too late to turn back. Either FDA accepted the application for licensing, despite these flaws, or refused it and sent ImClone back to the drawing board. As we all know, FDA chose the latter option.

Moreover, the due diligence performed by Bristol and the examination by the committee's scientific consultant of ImClone's pivotal study raise similar questions about whether Erbitux really works better in combination with another drug, or whether Erbitux truly has a clinically meaningful effect on colorectal cancer. I understand that ImClone and Bristol are planning to conduct additional studies on these issues and for the sake of cancer patients, I wish them well. But we now know that the promising response rates publicized by ImClone based on this study do not appear nearly as promising as they once did and may in fact be clinically and statistically meaningless.

Before receiving the refusal-to-file letter on December 28, 2001, ImClone had received signals from FDA as early as December 4 that a refusal-to-file letter was a realistic possibility given the concerns FDA had about ImClone's application. Certainly by December 20, after a phone call in which FDA told representatives of ImClone and Bristol to no longer contact the agency until it sent a decision letter on December 28, both ImClone and Bristol believed that a refusal-to-file letter was a probable result, according to interviews and records. In fact, on December 25, 2001, Brian Markison from Bristol called Harlan Waksal at ImClone to inform him that Bristol had confirmed from FDA that ImClone would be getting a refusal-to-file letter. The next day, ImClone sent a letter to FDA in an attempt to forestall the negative decision, and on December 27, Sam Waksal, ImClone's CEO at the time, personally called FDA in an attempt to stop the refusal-to-file letter. He was not successful.

Adding to the ImClone controversy, on that same day, December 27, and perhaps on December 28 as well, several family members and friends of Sam Waksal sold significant volumes of shares of ImClone stock, all prior to the public announcement of the FDA's December 28 refusal-to-file letter. For example, Sam's daughter, Aliza, sold $2.5 million of stock while she was on vacation. At the same time, Sam gifted to her twice the number of shares she had sold. Incidentally, the amount of these gifted shares was the same as the amount of shares that SEC now alleges that Sam Waksal moved from his own account but was unable to trade these shares through Aliza's account because broker-dealers refused to execute the trades without approval by ImClone's counsel.

In another example, Martha Stewart, who had been a long-time investor in ImClone and friend of Sam Waksal, sold all of what was left of her ImClone holdings on December 27. Phone records indicate a telephone call between Ms. Stewart and Dr. Waksal on that same date.

Yesterday, the SEC charged Sam Waksal with illegal insider trading, alleging that he had alerted certain family members about the refusal-to-file letter before it became public knowledge, who in turn sold large volumes of ImClone stock before the market learned of the negative FDA action.

In addition to the stock trading activity in late December of last year, the committee's investigation also reviewed the purchase and sale of ImClone stock by ImClone's directors and top executives during the months leading up to the Bristol $1 billion tender offer, which was consummated in October 2001. On October 29, 2001, 2 days before ImClone completed its application submission for Erbitux to FDA, Sam and Harlan Waksal, the founders and top executives of ImClone, sold approximately 1.4 million shares of ImClone stock to Bristol for about $111 million. However, unlike all the other ImClone shareholders who tendered shares to Bristol, the Waksals were helped in part by loans of about $35 million that they received from ImClone several months before, so that they could exercise their options to purchase ImClone stock at highly discounted prices.

These findings, and other information contained in the staff report and in our witnesses' testimony, will be of great interest to the

subcommittee. One of our chief concerns is assuring public confidence in our biotechnology/pharmaceutical industry and the FDA process. When there is a suspicion that we are not getting all the facts about a new drug, investment dries up and clinical trial enrollments stall. We must look seriously at whether the secrecy of the FDA approval process can be, or has been, abused and exploited for personal gain, and whether useful drugs are delayed because of flawed development strategies and internal FDA confusion.

The saga of failures like ImClone leads to a loss in confidence, not only in the possibilities of the science, but in the firms that seek to bring new cures to market and the public officials who must approve these cures and regulate these markets. My hope is that the lessons we draw from this debacle will enable us to provide improved direction to the companies, investors and the regulators who need to work cooperatively and openly if we hope to continue to bring the promise of science to the American people.

The Chair recognizes the gentleman, Mr. Stupak, for his opening statement.

[The prepared statement of Hon. James C. Greenwood follows:]

PREPARED STATEMENT OF HON. JAMES GREENWOOD, CHAIRMAN, SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS

In the past, when Americans of my generation have thought about the development of life-saving miracle drugs, the images most likely to come to mind have been those of self-effacing men of science like Alexander Fleming and Jonas Salk. In 1952, when Salk was convinced that he had developed a vaccine for the deadly scourge of polio, he didn't rush out to the marketplace with effusive praise either to the drugs efficacy or it's money making possibilities. Instead he vaccinated volunteers, including his wife and three sons. And only when it became clear that, even though the volunteers had developed antibodies to the disease, none had become ill, did he finally publish his findings, the following year, in the *Journal of the American Medical Association.* Now flash forward to 2001. Another Doctor, this time with a PHD in immunology, claims that his company is bringing another miracle drug to the market.

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  Yet, in an August 2000 meeting between ImClone and FDA to discuss this study, ImClone's proposed study design to support accelerated approval was deemed by FDA to be "probably acceptable."
- FDA's decision to accept the protocol design in effect overruled the initial recommendation of the primary FDA medical reviewer, who argued it failed to meet Federal requirements. Moreover, FDA's decision appears to be based on a significant misunderstanding as to the rigor of the study protocol—a misunderstanding that should have been quite apparent to ImClone from its discussions with FDA, but one ImClone did not seek to correct. As FDA reviewers examined the study more closely in the context of ImClone's formal licensing application, these protocol design issues finally received the attention they deserved, but by that point it was too late to turn back—either FDA accepted the application for licensing, despite these flaws, or refused it and sent ImClone back to the drawing board. As we all know, FDA chose the latter option.
- Moreover, the due diligence performed by Bristol, and the examination by the Committee's scientific consultant, of ImClone's pivotal study raise similar questions about whether Erbitux really works better in combination with another drug, and whether Erbitux truly has a clinically meaningful effect on colorectal cancer. I understand that ImClone and Bristol are planning to conduct additional studies on these issues and, for the sake of cancer patients, I wish them well. But we now know that the promising response rates publicized by ImClone based on this study do not appear nearly as promising as they once did, and may in fact be clinically and statistically meaningless.
- Before receiving the refusal-to-file letter on December 28, 2001, ImClone had received signals from FDA as early as December 4th that a refusal-to-file letter was a realistic possibility given the concerns FDA had about ImClone's application.

- Certainly by December 20th, after a phone call in which FDA told representatives of ImClone and Bristol to no longer contact the agency until it sent a decision letter on December 28th, both ImClone and Bristol believed that a refusal-to-file letter was a probable result, according to interviews and records.
- In fact, on December 25, 2001, Brian Markison from Bristol called Harlan Waksal at ImClone to inform him that Bristol had confirmed from FDA that ImClone would be getting a refusal-to-file letter. The next day, ImClone sent a letter to FDA in an attempt to forestall the negative decision, and on December 27th, Sam Waksal, ImClone's CEO at the time, personally called FDA in an attempt to stop the refusal-to-file letter. He was not successful.
- Adding to the ImClone controversy, on that same day, December 27th, and perhaps on December 28th as well, several family members and friends of Sam Waksal sold significant volumes of shares of ImClone stock—all prior to the public announcement of the FDA's December 28th refusal-to-file letter. For example, Sam's daughter, Aliza (A-leeza), sold $2.5 million of stock while she was on vacation. At the same time, Sam gifted to her twice the number of shares she had sold. Incidentally, the amount of these gifted shares was the same as the amount of shares that the SEC now alleges that Sam Waksal moved from his own account, but was unable to trade these shares through Aliza's account because broker-dealers refused to execute the trades without approval by ImClone's counsel.
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These findings, and other information contained in the staff report and in our witnesses' testimony, will be of great interest to the Subcommittee. One of our chief concerns is assuring public confidence in our biotechnology/pharmaceutical industry and the FDA process. When there is a suspicion that we are not getting all the facts about a new drug, investment dries up and clinical trial enrollments stall. We must look seriously at whether the secrecy of the FDA approval process can be—or has been—abused and exploited for personal gain, and whether useful drugs are delayed because of flawed development strategies and internal FDA confusion.

The saga of failures like ImClone leads to a loss in confidence, not only in the possibilities of the science, but in the firms that seek to bring new cures to market and the public officials who must approve these cures and regulate these markets.

My hope is that the lessons we draw from this debacle will enable us to provide improved direction to the companies, investors and the regulators who need to work cooperatively and openly if we hope to continue to bring the promise of science to the American people.

Mr. STUPAK. Thank you, Mr. Chairman—and also I think your opening statement certainly reviewed the investigation done by our respective staffs in this matter. I believe today's hearings raises a number of issues of importance to the Food and Drug Administration, the manufacturers of new drugs and biologics, investors, large and small, and most importantly the victims of cancer and their loved ones.

The ImClone story is not a happy one. We still do not know if Erbitux, a cancer drug developed by ImClone, will be a useful tool in the fight against colorectal and other cancers. Only good and

careful science, not anecdotal reports and certainly not inflated and inaccurate hype, will answer this question.

Last spring and summer, patients and their doctors were led to believe that a treatment for colorectal cancer, the second most prevalent, and one of the most deadly, was at hand, when the truth was that the drug had not been studied rigorously enough to determine what value Erbitux might have for the treatment of colorectal or other cancers. Erbitux does show activity and may yet prove to be another useful tool for some patients in the battle with a disease that is extremely resistant to treatment.

ImClone was in a position to understand how unlikely FDA approval was based on a registration study and another single arm study submitted last fall. But patients and oncologists were not informed that the proposed registration study was so incomplete and that despite six more months of trying, Bristol-Myers Squibb with all their expertise and resources has still not completed the residual work necessary for resubmission to the FDA.

Investors had no idea that ImClone was submitting, at best, a marginal application under an expedited procedure that must, and demands, rigorous standards and the conduct and reporting of the pivotal study and statistical power in the results. The ImClone application was so defective and the results were so inconclusive that any hope of an accelerated approval may have evaporated.

All this suggests that had the principals of ImClone decided that they would do a better design and a much better executed study instead of submitting a poorly designed and executed Phase II study, then cancer patients, their loved ones and the oncologists that treat them might have had Erbitux available this year.

Mr. Chairman, I believe that our respective staffs have done an excellent job. I believe that the staff has framed the issues accurately. I look forward to this hearing today. I look forward to answering questions, and I appreciate the work our staffs have done, and I think we owe them a great deal of gratitude bringing us up to date. I know they have worked on this for a long time. So I am ready to move on with this hearing. I will yield back the balance of my time.

[The prepared statement of Hon. Bart Stupak follows:]

PREPARED STATEMENT OF HON. BART STUPAK, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Today's hearing raises a number of issues of importance to the Food and Drug Administration (FDA), the manufacturers of new drugs and biologics, investors large and small and, most importantly, to the victims of cancer and their loved ones. The ImClone story is not a happy one. We still do not know if Erbitux, the cancer drug developed by ImClone will be a useful tool in the fight against colorectal and other cancers. Only good and careful science, not anecdotal reports and certainly not inflated and inaccurate hype will answer that question.

Last Spring and Summer, patients and their doctors were led to believe that a treatment for colorectal cancer, the second most prevalent and one of the most deadly forms of that disease, was at hand when the truth was that the drug had not been studied rigorously enough to determine what value it might have for the treatment of colorectal or other cancers.

Erbitux does show activity and may yet prove to be another useful tool for some patients in the battle with a disease that is extremely resistant to treatment.

ImClone was in a position to understand how unlikely FDA approval was based on the registration study and another single arm study submitted last fall. But patients and oncologists were not informed that the proposed registration study was so incomplete that despite six more months of trying, Bristol Meyers Squibb, with

all their expertise and resources has still not completed the residual work necessary for re-submission to FDA.

Investors had no idea that ImClone was submitting, to be generous, a marginal application under an expedited procedure that must require rigor in the conduct and reporting of the pivotal study and statistical power in the results. The ImClone application was so defective and the results were so inconclusive that any hope of accelerated approval has probably evaporated.

All of this suggests that had the principals of ImClone decided that they would do a better designed and much better executed study instead of merely submitting a poorly designed and executed Phase II study that they had on the shelf, the cancer patients, their loved ones, and the oncologists that treat them, might have had Erbitux available this year. Clearly, the sale of the company, not approval of the drug, was the Waksal priority.

Mr. Chairman, I believe that this investigation has been conducted properly and the staff has framed the questions accurately. I look forward to hearing the testimony and the response to the many questions yet to be answered.

Mr. GREENWOOD. The Chair thanks the gentleman and recognizes the chairman of the full committee, Mr. Tauzin.

Chairman TAUZIN. Thank you, Mr. Chairman. Mr. Chairman, I want to commend you again and the staffs of both sides of our committee for the excellent work in investigating this extraordinary story. The fact is that there are two stories here today. One of the stories will be more fully told by the SEC and the Justice Department as it examines how the FDA process and what appears to be some rather amoristic players conspired in a way that allowed insider trading to potentially occur and an awful lot of investors to lose a lot of money while insiders were trading on information that was available only to them in an attempt to cash out on what could be, and what was promised to be, a very promising drug for cancer patients.

The other story is about the process at FDA and how the FDA process allowed this to happen. And that story has more to do with cancer patients around America who lived with the hope, the expectation and the promise that Erbitux was everything it was hyped up to be and that it would be available by spring, right now, for cancer patients who are living only with this hope in mind, that finally something had been developed that would extend their lives. We were told, and Sam Waksal was one of those telling us, that Erbitux, according to him, and I quote, "is going to be huge. It is going to be one of the biggest drugs in the history of oncology, a drug that is going to alter the way that cancer therapy is done."

ImClone reported 400 calls a day from patients desperate to get Erbitux outside of clinical trials. And every indication was that the drug was not only everything it was promised to be but that it would be available by this spring. And the story that unfolds in our investigation is that while ImClone deserves a lot of credit over the years of research into these monoclonal antibodies, which may yet pay off 1 day for these patients, that the leadership of this company was apparently more intent on immediately cashing in on the promise that Erbitux held out for the patients instead of being carefully conscious of delivering on those promises sooner rather than later.

Erbitux had some pretty big names behind it and had the giants of the clinical oncology world on its board. It had John Mendelsohn and Vincent DeVita. And we learned in this investigation that the leadership of this company had total control over what information would be released to the public, about its own studies and about

the quality of this new product and about its potential since under our rules FDA is prohibited and restricted under Federal law from talking about such proprietary information. So we have a process whereby FDA is being restricted on what it can say about the clinical studies and about what is happening with this drug, while the company can go out and hype it and take advantage of it financially, while at the same time, according to our investigation, recognizing all the while that its studies were flawed and there were problems with the FDA approval process.

Now that is the sad story. The saddest story is not about investors losing money or about the fact that some of these people are facing now SEC and Justice Department investigations and, as we have learned just recently, indictments. The sad thing is that our investigation is opening the black box of the FDA process for public review, and what we see is a drug development and FDA review system that is not necessarily serving the best interest of America's people and its cancer victims in this case.

Now, our job, Mr. Chairman, is primarily to examine that process, to see how this train wreck occurred and to see why the promise of a drug that could still hold such great hope for cancer patients was denied them because of a process that fell apart like this; instead yielded only financial gains to people who took advantage of it. If we end up with a process where drug approval strategies don't work in the interest of our patients in America, but simply allow companies to hype their stock and personally enrich their executives and shortchange their clinical research in the process, and if we have an FDA that sort of hangs back while the company falls on its face with such a high risk approval strategy, as was developed in this case, then it is not just the company who loses the gamble, it is the American public who loses, and most importantly the cancer patients who really by this spring, by now, were led to believe that there was really something great on the horizon that would be available now for them and give them life and hope.

Now, we have got to fix this system, and if your hearings point the way for FDA and for us, we in the Congress, who have jurisdiction in this area to make some changes to make sure this kind of a train wreck doesn't happen again, we will leave it to the Justice Department and the SEC to deal with the miscreants here, but we ought to give cancer patients who are desperate for hope in a drug like Erbitux a chance to have it really tested and proven out. And if it is as good as some people think it is, that they have the advantage of having it in the marketplace and available to them before it is too late. And that is the task, that is the task of this committee, and I commend you for taking it on. I yield back.

[The prepared statement of Hon. W.J. "Billy" Tauzin follows:]

PREPARED STATEMENT OF HON. W.J. "BILLY" TAUZIN, CHAIRMAN, COMMITTEE ON ENERGY AND COMMERCE

Thank you, Chairman Greenwood, and let me commend you for holding this hearing on ImClone Systems and its much touted "miracle" cancer drug, Erbitux. We have much to learn from the story of this drug. And I believe the story of this drug provides an opportunity to examine the drug development and FDA review systems. We need to make sure these systems work for patients.

Cancer patients and their families had great hopes that Erbitux would be on the market by now. They and the media believed all that was asserted by ImClone and its prominent backers. ImClone's CEO, Sam Waksal, promised that "Erbitux is

going to be huge. It is going to be one of the biggest drugs in the history of oncology—a drug that is going to alter the way cancer therapy is done."

Imagine what cancer patients thought when they heard that statement. ImClone reportedly received 400 calls a day from patients desperate to get Erbitux outside of clinical trials. By late last fall—when ImClone filed its application with the FDA—there were very sick colon cancer patients holding onto hope that Erbitux would be on the market by this Spring—by now. But when ImClone's clinical research package was finally unveiled to the FDA, it had so many problems, the FDA could not even review it.

ImClone certainly deserves credit for its years of research into monoclonal antibodies, which still may pay off for patients in the future. Unfortunately, when the company should have been paying more attention to the quality of its clinical trials, its leadership appeared more intent on immediately cashing in on Erbitux's promise—and delivering for cancer patients later, if ever.

ImClone had the selling points to boost its stock and raise the hopes of dying cancer patients. Erbitux is a targeted therapy, and targeted therapy is supposedly the future of cancer treatment. It had the names, the giants of clinical oncology on its board—John Mendelsohn, Vincent DeVita. It had a growing anti-cancer drug market. And, most important, it had virtually total control over what information would be released to the public about its studies since the FDA is restricted under Federal law from talking about such proprietary information.

Yet it appears, as our Committee investigation has revealed, that ImClone was so excited by preliminary response rates in very sick colon cancer patients, it tried to take a mediocre clinical trial and gussy it up as a study worthy of an accelerated approval by itself. But when it became crunch time to get FDA approval, the failure of ImClone's key executives to ensure the quality of its clinical trials collided with the hype. And, all the while, ImClone's insiders were lining their own pockets with millions, as ImClone's publicly-traded stock soared on false, public promises.

Now the SEC has alleged that Sam Waksal knew about the FDA's refusal-to-file letter two days before it was issued and that he tipped off family members who sold $10 million of ImClone stock. As Vee Kumar, a 47-year school psychologist and colon cancer patient from Kirkland, Washington, told *Vanity Fair* magazine: "There is no excuse for raising patients' hopes and then not delivering. There's been a lot of talk about ImClone's monetary rewards from Erbitux, but not enough about getting it to the patients who need it. They really ought to have done their homework better."

I understand that the preliminary Committee staff report reveals additional problems in the clinical package ImClone submitted to the FDA, and lays out the series of actions by ImClone, its strategic partner Bristol-Myers Squibb, and FDA that led to this debacle. This Committee's investigation opens the black box of the FDA process, and reveals a drug-development and FDA review system that is not serving the interests of the American people.

Through this inquiry, I hope we can prevent such train wrecks in the future. Drug companies and the FDA should develop drug approval strategies that work in the patient's interest—not so that companies can hype stock, personally enrich executives, and short-change clinical research; not so that the FDA hangs back while a company falls on its face with a high-risk approval strategy, as if it's just the company's gamble. It may be the company's gamble, but if it fails, cancer patients are the ones who really lose.

Mr. Chairman, I look forward to working with you to improve the drug development system and to make that system really deliver for our sickest patients.

Mr. GREENWOOD. The Chair thanks the chairman and recognizes, for 3 minutes for purposes of an opening statement, the gentlelady from Colorado, Ms. DeGette.

Ms. DEGETTE. Thank you so much, Mr. Chairman. The case of ImClone presents what seems to have become a parable for our times: an upstart corporation with tremendous financial promise, corporate executives reaping fantastic financial, soaring stock prices, in this case up to $70 a share, a precipitous fall causing the stock to plummet tenfold back down to $7, allegations of insider trading by the officers of the company and their close friends. But here is the difference here, and I agree but I disagree a little with my chairman because I don't think it is a second story, I think it is an interwoven story that relates directly to all the things I just listed, and that is tens of thousands of cancer patients who are

hanging on to the thread of a hope that Erbitux would be added to the two existing therapies for deadly colorectal cancer. The foibles of the key players here, corporate executives, researchers and FDA reviewers, did not just result in tremendous financial losses to investors but also devastated cancer patients' hopes.

Nowhere else in the world is there a greater confluence of pharmaceutical/biotech industry growth, shareholder expectation of large profit margins, high hopes among patients for new and innovative therapies and confidence among the American people that the appropriate regulatory agency, the Food and Drug Administration, is providing the appropriate oversight.

To address at least two of these issues, quick approval of new and innovative therapies and government oversight of the process, Congress established an accelerated approval process as part of the 1997 Food and Drug Administration Modernization Act, or FDAMA, which was a comprehensive overhaul of the Nation's food, drug and medical device laws. The Fast Track approval process was created for getting therapies that demonstrate the potential to help dying patients to the marketplace quickly. While the Fast Track process bypasses the rigors of a large-scale Phase III trial, it should not and must not allow products to bypass rigorous and sound scientific review. Unfortunately, there seems to be evidence that this is exactly what happened in the case of Erbitux.

It appears that too many people dropped the ball throughout the approval process in this particular case, from the executives and scientists at ImClone who designed the flawed clinical trials, to Bristol-Myers Squibb, ImClone's business partner, who was aware of the trial's flaws, including the too small sample size, and enrollment of patients who did not meet the eligibility criteria. From the FDA's mishandling of the study's protocol design to the issuance of the refuse-to-file letter, sloppy work abounded throughout this process and no one is without blame. I can assure you that all of our votes for FDAMA were not made with the intent of relaxing the rules.

However, what dismays us the most is this impact this case may have on other therapies that will be seeking Fast Track approval in the future, including this therapy, by the way, therapies that could have the potential cure for millions of people or even just extend their lives for another day, a month or a year. Like many of my colleagues, I receive hundreds of letters every year from constituents asking to facilitate quick FDA approval for therapies, therapies like for multiple myeloma and thalidomide, therapies for irritable bowel syndrome or lontronix and on and on.

I am sympathetic to these patients. On the other hand, the United States has perhaps the world's most stringent standards for approving new drugs. We cannot shirk our duty to take a long, hard look at the approval process. Our job, Mr. Chairman, as I see it today, is to examine how we can foster speedy approval of new drugs, especially in cases where there are few alternatives, while at the same time ensuring that they are safe and effective. I yield back.

[The prepared statement of Hon. Diana DeGette follows:]

PREPARED STATEMENT OF HON. DIANA DEGETTE, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF COLORADO

The case of ImClone presents what seems to have become almost a parable for our times:

—An upstart corporation with tremendous financial promise;
—Corporate executives reaping fantastic financial gains;
—Soaring stock prices;
—A precipitous fall—causing the stock to plummet ten-fold;
—Allegations of insider trading by the officers of the company and their close friends.

But here's the difference: Tens of thousands of cancer patients were hanging on to the thread of a hope that Erbitux would be added to the two existing therapies for deadly colo-rectal cancer. The foibles of the key players here—corporate executives, researchers, and FDA reviewers do not just result in tremendous financial loses to investors, but devastated cancer patent hopes. Our job as I see it today, is to examine how we can foster speedy approval of new drugs, especially in cases where there are few alternatives, while ensuring their efficacy.

No where else in the world is there a greater confluence of pharmaceutical/biotech industry growth, shareholder expectation of large profit margins, high hopes among patients for new and innovative therapies and confidence among the American people that the appropriate regulatory agency, the Food and Drug Administration is providing the appropriate oversight.

To address at least two of these issues, quick approval of new and innovative therapies and governmental oversight of the process, Congress established an accelerated approval process as part of the 1997 Food and Drug Administration Modernization Act (FDAMA), a comprehensive overhaul of the nation's food, drug and medical device laws.

The "fast track" approval process was created for getting therapies that demonstrate the potential to help dying patients to the marketplace quickly. While the fast track process bypasses the rigors of a large-scale phase III trial, it should not, and must not, allow products to bypass rigorous and sound scientific review. Unfortunately, there seems to be evidence that this is exactly what happened in the case of Erbitux.

It appears as though too many people dropped the ball throughout the approval process in this particular case. From the executives and scientists at Imclone who designed the flawed clinical trials, to Bristol Myers Squibb, Imclone's business partner who was aware of the trial's flaws including the too small sample size, and enrollment of patients who did not meet the eligibility criteria. From the Food and Drug Administration's mishandling of the study's protocol design to the issuance of the refusal to file letter, sloppy work abounded through this process.

I can assure you that my vote for passage of FDAMA was not made with the intent of relaxing the rules, and I'm sure my colleagues that sit here with me today have the same sentiment. By no means did the '97 Act include a relaxation of any of the rules. There was nothing in it that came close to subverting rigorous reviews of the scientific merits of protocols.

However, what dismays me most is the impact that this case may have on other therapies that will be seeking fast track approval in the future. Therapies that could have the potential cure for millions of people, or even just extend their lives for another day, a month, a year.

Like many of my colleagues, I receive hundreds of letters each year from constituents asking me to help facilitate quick FDA approval for the one therapy that might be able to ease their pain, or extend their own, or a loved one's, life.

For instance, I have received letters from sufferers of diseases such as multiple myeloma, an incurable form of blood cancer, who are desperate for Thalidomide, a drug with a long history associated with birth defects. Just the other day I got a letter from a constituent who suffers from irritable bowel syndrome pleading that I do everything I can to facilitate the return of Lotrinex to the market.

I am very, very sympathetic to these people both as their elected representative, and in my capacity as a public servant who votes on legislation that effects every single person in this country. They are looking to us to facilitate the approval of effective and safe medications. And for good reason. The United States has perhaps the world's most stringent standards for approving new drugs. We cannot shirk our duty to take a long hard look at the approval process.

Mr. GREENWOOD. The Chair thanks the gentlelady and recognizes for 3 minutes for an opening statement the gentleman from Kentucky, Dr. Fletcher.

Mr. FLETCHER. Thank you, Mr. Chairman. I think you have reviewed certainly the situation well. I appreciate very much you holding this hearing. Your statements, as well as the chairman of the full committee, certainly reflect my feelings. And in the interest of time and moving on, I would like to submit my opening statement to the committee, if that is okay.

Mr. GREENWOOD. The gentleman's statement will be made part of the record.

[The prepared statement of Hon. Ernie Fletcher follows:]

PREPARED STATEMENT OF HON. ERNIE FLETCHER, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF OKLAHOMA

Chairman Greenwood; thank you for having this hearing today.

As a physician I have seen the devastation that Cancer can cause. I have seen the emotion and physical destruction that this disease brings to patients and their families.

In the US where we have one of the best healthcare systems in the world, there will be more than 1.2 million new cancer cases diagnosed in 2002. This year about 555,000 people will die from cancer.

It is no surprise that patients and physicians are excited when a promising new drug or therapy becomes available. The Energy and Commerce Committee has worked hard to see that groundbreaking research can provide physicians with the tools to provide treatment for cancer.

While new drugs, Like Erbitux show great promise, we must also balance their development with the public's interest. They must be proved safe and effective before they are available for general use. We need to make sure that the FDA is doing the best job possible to balance these two issues. This hearing needs to look closely at how this particular drug was handled and use that information to develop policy that allows these new technologies to be available to patients as quickly and safely as possible.

Mr. GREENWOOD. The Chair recognizes the gentleman from Illinois, Mr. Rush, for an opening statement, for 3 minutes.

Mr. RUSH. Thank you, Mr. Chairman. Mr. Chairman, I am very glad and happy that you are convening this hearing. I want to submit my full statement for the record and beg leave to present my full statement for the record. But I also want to state to you, Mr. Chairman, and to others who have gathered here, to the entire subcommittee, that I am here with an open mind. I have not reached any conclusions, I am not faulting any participant at this point in time. I believe that this hearing will lead me in a direction where I will be able to determine for myself exactly what the problem is, what happened in this particular case, in the case of Enron. And I will be able to determine what I think is the appropriate way to deal with this, both at the FDA and also in any other governmental body. So I am here with an open mind, and I want to see exactly and hear for myself what the issues are and who is at fault, if there is anyone at fault in this particular case. Thank you, and I yield back the balance of my time.

Mr. GREENWOOD. The Chair thanks the gentleman and recognizes, for 3 minutes for an opening statement the gentleman from Florida, Mr. Stearns.

Mr. STEARNS. Thank you, Mr. Chairman. Of course, thank you for holding this hearing today. The United States is the foremost in the world today in biotechnological and pharmaceutical innovation. It is unfortunate this scandal has created in the minds of the public some trepidation. This is one more scandal we have seen up here this year with the Enron and Tyco and others, and the real

question is, I think, how could analysts and consumers be sure when they are investing in these stocks where you have this executive, Sam Waksal, running around, hyping his Erbitux as the blockbuster cancer drug of all time, of the future, and meanwhile he is mortgaging his shares for an $80 million loan? He is also getting other loans that we can't determine completely. But how can the investor and the analyst look at this company and decide whether or not this man is hyping this for other reasons other than its true picture of the drug? At the same time, he is submitting applications to the FDA which do not have all the clinical evidence.

So I am approaching this, Mr. Chairman, from the standpoint of the consumer and the investor: How can he or she be sure when they are investing in this corporation which is talking about a blockbuster drug that the money that is being exercised by the CEOs and the other investors who control the corporations is being properly displayed, made public and coincides with their activities?

So we have a history this year of several scandals. We need to follow the money, we need to understand what his previous activities were at the same time he is hyping this Erbitux drug, and we need to protect the consumers, because in the end the consumer is sitting out there thinking that the CEO is correct. At the same time, the CEO has another ulterior motive. So if somehow this hearing would bring to bear a better understanding of what is more transparency on the P&L statement and could help consumers to understand whether they should continue investing, I think that would help bring more confidence to the market. And, you can never be too skeptical. I think that is what has happened here. And you can never be too diversified in the sense that you are dealing with these highly volatile stocks where you have the CEOs and their family hyping this thing at the same time they are trying to sell off their stock knowing inside information. So I commend you for this hearing, and I look forward to the testimony.

[The prepared statement of Hon. Cliff Stearns follows:]

PREPARED STATEMENT OF HON. CLIFF STEARNS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF FLORIDA

Mr. Chairman, thank you for holding this hearing today. The United States is foremost in the world today in biotechnological and pharmaceutical innovation. We boast the leadership role in the world in new, lifesaving discoveries. For this, we can thank many parties: capital-providing shareholders who fund the research; the brilliant scientists and support staff of firms toiling at the bench to develop new cures and treatments; the Food and Drug Administration regulators and approvers who carefully examine submissions for accuracy and worthiness. When a drug is on the FDA fast-track for approval because it may be patients' last hope at a cure for a life-threatening condition like cancer or AIDS, the proper functioning of the system becomes all the more imperative.

For this system to work, there needs to exist complete honesty and integrity in a company's operations. Yesterday (June 12), we learned that the CEO of the company visiting us today, Samuel Waksal of ImClone, evidently learned of the FDA's negative decision on ImClone's flagship drug undergoing approval, Erbitux. According to the Securities and Exchange Commission (SEC), Waksal and his relatives sold greater than $10 million in Imclone stock in a period of 48 hours: on December 26 and December 27—a day before the FDA released its "refuse-to-file" letter to ImClone on December 28. Further, Dr. Waksal's brother, Harlan, we learn, sold roughly $50 million worth of shares on December 6, a day after FDA officials first indicated a negative review of the application may be forthcoming. Further financial improprieties are the fact that ImClone lent money to insiders through the exercise of options based on ongoing, but not yet publicly disclosed, discussions with collaborating pharmaceutical firm Bristol-Myers Squibb. As many of us have know, execu-

tive compensation via options lacks clear and consistent definitions that potential investors and lenders need to make solid decisions. Options are an exercise in creativity, in the place of quantifiable, sound accounting.

In addition to options, SEC lawsuit documents reveal that Dr. Sam Waksal was carrying more than $80 million in debt at the time of the FDA's Erbitux announcement. Could this have been another motive in quickly dumping his stock, leaving the rest of the investors to hold the bag?

Shady executive practices lead to damaging effects rippling through the economy: *Integrity is the elixir that will attract capital and lead to lifesaving innovation, while deceit is the poison that is eroding investor confidence.*

This hearing today should open up all these processes and players for exploration into whether the drug development and approval, including its financing, is occurring as intended. Are the delicate balances between patient safety, shareholder reward, and company incentive all aligned, or is the scale tipped too heavily in favor one way or another, in need of adjusting? Is the exchange between necessary confidentiality and public disclosure at an optimum?

That is why on this Committee are here today, in our investigative capacity and responsibility to American citizens.

We are here to find out: What are the *facts*? What happened? What is *supposed to* happen? What did the high-level executives and their cronies know and when? If something went wrong, how can it be corrected to safeguard the balance I just described among patients, the firm, and the shareholders? Let us fairly and open-mindedly listen to our witnesses today, and thank you.

Mr. GREENWOOD. The Chair thanks the gentleman and recognizes, for 3 minutes for an opening statement, the gentleman from North Carolina, Mr. Burr.

Mr. BURR. Thank the Chair. And, clearly, the chairman has not only tremendous interest in this, he has shown in the past tremendous interest in the FDA process. The difficulty that we deal with in this particular case is that many of us, years ago, saw the potential pitfalls of the emergence of biotechnology companies in this country, that without a clear road map at the FDA as to how to evaluate that industry, we saw the tendency of venture capital that funded these companies that hadn't proved anything when they emerged other than that they were creative and they thought they might be on the track to a breakthrough, that with enough capital and enough time that they might unlock that key to something magical and eventually make it through an FDA process. We, in 1997, helped to make that process a little more predictable and we thought a little more transparent. We learn with everything hearing that it is not quite as clear as what we intended to be, and we, as Members of Congress, have tremendous work left.

But I think that it is extremely important for us to never forget this is about patience, that though we talk about publicly or privately held companies, in every case their quest is to come up with a new compound that treats something that today is untreatable. I am not sure the percentages today of efforts of the pharmaceutical or biologic world that actually come to fruition, but there are many more paths that they go down that don't prove to be successful, that never make it into the trial process where money is invested, in good faith, money by that company, whether it is public or private, because they believe that that might be the avenue to unlocking the key—the key to unlocking the disease.

We are not here to judge the business decisions of any companies. Ours is to make sure that there is a process, a process that not only the companies but the investors can have confidence in works. I am hopeful, Mr. Chairman, that the FDA will be very honest to us today as to how the protocols could have been flawed, how

they could have been designed in a wrong way. If the information was bad, then maybe we need to go back, Jim, and look at whether we change what we did. We thought we got it as close to right as we could.

The fact is that we are where we were 5 years ago. We are sitting in a committee hearing, and we have got people pointing fingers at each other, and the person that loses are the patients with colorectal cancer. Diana DeGette laid it out very, very well. Everybody is blaming somebody but there is one real specific group that is left behind. As a Member of Congress, I think it is extremely important that we listen very closely to BMS, because they apparently saw something that was worth a tremendous amount of money on the part of their investors in this company but more important in Erbitux, and my understanding is that their hopes have not changed. If their hopes have not changed, then our hopes have not changed that there may be a key that unlocks something here, but more importantly that we must make sure that the system works in a way that we nurture other biotechnology companies to continue to search for those breakthroughs and not quit because of another problem. I thank the Chair for his commitment, and I yield back.

Mr. GREENWOOD. The Chair thanks the gentleman and recognizes for 3 minutes for an opening statement the gentleman from Ohio, Mr. Gillmor.

Mr. GILLMOR. Thank you, Mr. Chairman. I have a very profound and interesting opening statement, but in the interest of time I will submit it for the record. Thank you.

[The prepared statement of Hon. Paul Gillmor follows:]

PREPARED STATEMENT OF HON. PAUL E. GILLMOR, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF OHIO

Thank you, Mr. Chairman. Prescription drugs are increasingly prevalent and influential on our health care system. With an ever-increasing number of drugs pending approval by the Food and Drug Administration, we cannot ignore the important, time-consuming process that is involved in making a drug available to market.

In the case of Imclone Systems, alleged impropriety has taken place in its application for approval of the cancer drug Erbitux. Although the drug has proven successful in a variety of cases, questions over its consistency and a hastily prepared application contributed to the FDA's rejection of this drug. That is why we are holding this hearing today.

In the case of ImClone, however, the FDA has been criticized for its ruling. By applying a more rigorous standard to Erbitux application, it has violated the spirit of "Fast Track" approval. Furthermore, it has been alleged that ImClone CEO Samuel Waksal had prior knowledge of the likely rejection of this drug from FDA employees, who are represented today. As a result, significant insider trading took place just days before the final FDA ruling, enriching several Waksal family members and other well-known shareholders. Although it is not in the purview of this Committee to investigate such trading deals, it does fall under the jurisdiction of the SEC and the Financial Services Committee, on which I do serve.

I will look forward to witness testimony today that will hopefully shed light on the FDA approval process, as well as alleged impropriety by Imclone that has left shareholders with substantial losses. Upon hearing testimony, I am confident that this Committee will have a better idea on how to address and reform the operations of the FDA for the 21st century.

Mr. GREENWOOD. The Chair will check and if it is profound, it will be included in the record.

And with that, the Chair calls forward the first panel of witnesses, and they are Dr. Frank Papineau, who is a detailee—

Papineau, I am sorry, Papineau, Dr. Frank Papineau, who is a detailee, working for the Committee on Energy and Commerce, and accompanying him, Dr. Raymond Weiss, who is a consultant in oncology, a clinical professor of Medicine at the Lombardi Cancer Center of Georgetown University Medical Center here in Washington.

Welcome, gentlemen. Thank you for your appearance. You are both aware that this committee is holding an investigative hearing and when doing so we have had the practice of taking testimony under oath. Do either of you have objections to giving your testimony under oath? Seeing no such objection, the Chair advises you that under the rules of the House and the rules of the committee, you are entitled to be advised by counsel. Do you desire to be advised by counsel during your testimony today? Okay. Then if you will stand and raise your right hand, I will swear you in.

[Witnesses sworn.]

Okay. You are under oath, and Mr. Papineau, we will begin with you. You are recognized for your testimony.

TESTIMONY OF FRANK PAPINEAU, DETAILEE, COMMITTEE ON ENERGY AND COMMERCE; AND RAYMOND WEISS, CONSULTANT IN ONCOLOGY, CLINICAL PROFESSOR OF MEDICINE, LOMBARDI CANCER CENTER

Mr. PAPINEAU. Chairman Greenwood, ranking member and members of the subcommittee, I am Frank Papineau, on detail to the Energy and Commerce Committee's staff. I am here today to provide background information and key facts and dates surrounding the Food and Drug Administration's decision to end its consideration of ImClone Systems' highly touted cancer drug, Erbitux, and the questionable ImClone stock-selling activity during that timeframe.

My remarks are an oral summary taken from the committee staff report provided for today's hearing. I am accompanied today by Dr. Raymond Weiss, consultant in Oncology and clinical professor of Medicine at Georgetown University Medical Center. Dr. Weiss is under contract with the committee to provide assistance to the staff. Dr. Weiss wrote a report, and his findings are appended to the committee staff report.

By way of background, ImClone Systems is a small biotech company based in New York City, founded in 1984 by two brothers, Sam and Harlan Waksal. ImClone has never turned a profit in its 18 years of existence and reportedly has spent over $200 million on research of Erbitux. Many people involved in cancer research believe that Erbitux is a promising drug and widely expected it to be on the market this year. Erbitux, however, was not approved for the market because the Food and Drug Administration found so many problems with Erbitux's application for approval that it issued a refusal-to-file letter, a rare FDA action that effectively turned the drug back to the company for further study. This situation attracted national attention because of the pre-market publicity about the drug, because of ImClone's record-setting $2 billion alliance with Bristol-Myers Squibb to market Erbitux and because of the multi-million dollar stock trades by ImClone insiders in the weeks before generated a negative decision.

Before we proceed to the business dealings, let me first highlight two of the staff's findings regarding FDA's review of Erbitux. One, FDA's initial decision in August 2000 to grant Fast Track designation to Erbitux appears to have been based on incorrect information regarding the study protocol submitted by ImClone in support of the proposed cancer treatment which involved Erbitux and another cancer drug, Irinotecan. Two, FDA made the initial decision before it had full information about Erbitux's activity when administered in the absence of the other drug, and it was the other information, requested in a letter by FDA in January 2001 and received from ImClone in October 2001, that led the agency reviewers to conclude the application was incomplete.

In early 2001, Bristol-Myers Squibb failed in its effort to form an alliance with a biotech company called OSI that it believed had a promising cancer drug. The company believed it was losing its share of the oncology drug market and decided to revisit ImClone and its cancer drug, Erbitux. On June 1, 2001, after a month of negotiations, Sam Waksal outlined an acquisition that would give Bristol Myers a 70 percent majority stake in ImClone. Bristol's Board of Directors rejected the deal. Dr. Waksal then told Bristol that he was willing to consider alternative proposals provided they include a significant equity investment in ImClone by Bristol, and he also advised Bristol that he believed ImClone's existing stockholders would benefit most if Bristol acquiring equity interest through a tender offer to the ImClone's existing stockholders.

During July 2001, after ImClone was virtually assured of an equity deal and in anticipation of the tender offer from Bristol, ImClone's board agreed to lend $35.2 million to the Waksal brothers and the chairman of the board. The loans were unsecured and at an interest rate of 7.75 percent. The loans provided an opportunity for the three individuals to exercise options and warrants they held to purchase a total of 4.5 million shares of ImClone stock. Sam Waksal and Harlan Waksal's loans were $18.2 million and $15.7 million respectively. The chairman's loan was in the amount of $1.2 million.

On October 29, 2001, thousands of ImClone's shareholders participated in the Bristol tender offer to purchase ImClone stock at $70 a share, a $20 premium over the trading price. ImClone's Board of Directors tendered 2.1 million shares to Bristol by themselves, representing 15 percent of the stock tendered by ImClone shareholders. Sam and Harlan Waksal tendered 814,674 and 776,450 shares for about $111 million themselves. Simply stated, this means that the Waksal brothers received more than 10 percent of the entire proceeds paid by BMS during the tender offer. Although all ImClone shareholders were allowed to tender shares to BMS, only the Waksals and two other board members borrowed millions of dollars of company funds to purchase the stock and then tender it to Bristol.

On December 28, 2001, the FDA issued a refusal-to-file letter in response to the ImClone submission. The RTF letter is sent in rare cases when a submission is deemed insufficient. It is a non-public document containing trade secrets and confidential commercial information. In a December 31, 2001 conference call with investors, ImClone executives said that FDA sent the RTF letter because the

Erbitux application was missing certain "train of documentation" information needed by regulators to accept the filing. ImClone said it would be able to answer the FDA questions by the end of the first quarter, leading hopefully to Erbitux being approved by the fall of 2002.

On January 4, 2002, the Cancer Letter published excerpts of the RTF letter indicating, contrary to ImClone statements to investors, FDA had a long list of concerns that went far beyond record keeping. The FDA believed ImClone' clinical trial was not adequate and well controlled and that additional studies would be needed. The letter suggested FDA had warned ImClone starting in August 2000 that its data would have to demonstrate that Irinotecan, the standard chemotherapy mentioned above, was needed along with Erbitux. But the data submitted by ImClone was not sufficient to distinguish the effects of the two treatments.

Adding to the controversy over Erbitux has been the trading of ImClone stock by ImClone insiders a few weeks before the FDA letter, as well as trading of stock by Waksal family relatives and friends during the 48 hours before the FDA letter was issued. On December 21, 2001, ImClone issued a Company order stopping employees from trading in ImClone stock until the FDA decision on Erbitux was made public. The committee staff believed until yesterday that no member of the board or officer of the company traded stock between the 21st and 28th.

The staff found that, except for Sam and Harlan Waksal, members of Sam Waksal's immediate family sold ImClone stock on December 27, 2001 or the next day, hours before ImClone announced publicly that FDA had refused to accept the filing of Erbitux. We found that three officers of ImClone sold stock prior to December 18, 2001 on the advice of their broker. In addition, Harlan Waksal conducted a forward sale of 700,000 shares on December 6, 2001.

The staff learned that on October 31, 2001, Harlan notified the ImClone board members that he planned to execute a $700,000 sales transaction. He told the board that the stock would still be under his voting control for the next 3 years. He also stated he would finalize the transaction over the next 2 weeks. He told the committee staff in early 2001 he attempted to shop the sale. He told the staff he was forced to sell the ImClone stock to come up with enough cash to pay substantial taxes racked up from his prior exercise of stock options and the tendering of shares to Bristol. He also stated that because he didn't want to sell shares he entered into a forward sales contract that gives him a percentage of the cash value of the shares up front but still allows him to control the shares and defer tax payments for another 2 years. In short, Waksal received less than the stock was worth at the time of the sale, but he also limited the downside risk when ImClone's stock price continued to drop. It should be noted that Harlan Waksal sold the 700,000 shares on the same day that ImClone hit its 52-week high.

Mr. Chairman, that concludes my prepared statement. I'll be happy to answer any questions.

[The prepared statement of Frank Papineau follows:]

PREPARED STATEMENT OF FRANK PAPINEAU, COMMITTEE STAFF, COMMITTEE ON ENERGY AND COMMERCE

Chairman Greenwood, Ranking Member Deutsch, and Members of the Subcommittee, I am Frank Papineau, on detail to the Energy & Commerce Committee's staff. I am here today to provide you with background information and key facts and dates surrounding the Food and Drug Administration's decision to end its consideration of ImClone Systems' highly touted cancer drug, Erbitux, and the questionable ImClone stock-selling activity during this turn of events.

My remarks are an oral summary taken from the Committee staff report prepared for today's hearing. I am accompanied today by Dr. Raymond Weiss, Consultant in Oncology and Clinical Professor of Medicine at Georgetown University Medical Center. Dr. Weiss is under contract with the Committee to provide assistance to the staff. Dr. Weiss wrote a report of his findings, which is appended to the Committee staff report.

BACKGROUND

By way of background, ImClone Systems is a small biotech company based in New York City, founded in 1984 by two brothers—Sam and Harlan Waksal. ImClone has never turned a profit in its 18 years of existence and reportedly has spent over $200 million on research of Erbitux. Many people involved in cancer research believe that Erbitux is a promising drug and widely expected it to be on the market this year. Erbitux, however, was not approved for the market because the Food and Drug Administration found so many problems with ImClone's application for approval that it issued a Refusal To File letter, a rare FDA action that effectively turned the drug back to the company for further study. This situation attracted national attention because of the pre-market publicity about the drug, because of ImClone's record-setting $2 billion alliance with Bristol-Myers Squibb to market Erbitux, and because of multi-million dollar stock trades by ImClone insiders in the weeks before FDA's negative decision.

Over the past six months, Committee staff has conducted an extensive investigation into matters surrounding ImClone's cancer drug and related business dealings. The Committee's investigation focused on the FDA drug approval process, Erbitux's clinical trials, Bristol-Meyer's partnership arrangement to acquire commercial rights to Erbitux, and the key events leading up to FDA's Refusal to File letter and trading of ImClone stock by its board members and officers, as well as, several of Sam Waksal's immediate family and friends.

Before we proceed to the business dealings, let me first highlight two of staff's findings regarding FDA's review of Erbitux: One, FDA's initial decision in August 2000 to grant fast-track designation to Erbitux appears to have been based on incorrect information regarding the study protocol submitted by ImClone in support of the proposed cancer treatment, which involved Erbitux and another cancer drug, Irinotecan. Two, the FDA made this initial decision before it had full information about Erbitux's activity when administered in the absence of this other drug; and it was this other information—requested in a letter by FDA in January 2001 and received from ImClone in October 2001—that led agency reviewers to conclude the application was inadequate.

THE BRISTOL-MEYERS SQUIBB DEAL AND IMCLONE'S INTERNAL LOAN

In early 2001, Bristol-Meyers Squibb (BMS) failed in its effort to form an alliance with a biotech company, OSI, that it believed had a promising cancer drug. The company believed it was losing its share of the oncology drug market and decided to re-visit ImClone and its cancer drug Erbitux. On June 1, 2001, after a month of negotiations, Sam Waksal outlined an acquisition plan that would give BMS a 70% majority stake in ImClone. BMS's Board of Directors rejected the deal. Mr. Waksal then told BMS that he was willing to consider alternative proposals provided they include a significant equity investment in ImClone by BMS and he also advised BMS that he believed ImClone's existing stockholders would benefit most if BMS acquired an equity interest through a tender offer to the ImClone's existing stockholders.

During July 2001, after ImClone was virtually assured of the equity deal and in anticipation of the tender offer from BMS ImClone's Board agreed to lend $35.2 million to the Waksal brothers and the Chairman of the Board. The loans provided the opportunity for the three individuals to exercise stock options and warrants they held to purchase a total of approximately 4.5 million shares of ImClone stock. (Sam Waksal and Harlan Waksal's loans were $18.2 and $15.7 respectively. The Chairman's loan was in the amount of $1.2 million.)

On October 29, 2001, thousands of ImClone's shareholders participated in the BMS tender offer to purchase ImClone stock at $70 a share, a $20 premium over the trading price. ImClone's Board of Directors tendered 2.1 million shares to BMS by themselves—representing approximately 15% of the stock tendered by ImClone shareholders to BMS. Sam and Harlan Waksal tendered 814,674 and 776,450 shares for about $111 million. Simply stated this means that the Waksal brothers received more than 10% of the entire proceeds paid by BMS during the tender offer. Although all ImClone shareholders were allowed to tender shares to BMS, only the Waksals and two other board members borrowed millions of dollars of company funds to purchase the stock and then tender it to BMS.

THE RTF LETTER

On December 28, 2001, the FDA issued its "refuse-to-file" (RTF) letter in response to the ImClone submission. The RTF letter is sent in rare cases when a submission is deemed insufficient. (It is a non-public document containing trade secret or confidential commercial information.) In a December 31, 2001 conference call with investors, ImClone executives said that FDA sent the RTF letter because the Erbitux application was missing certain "train of documentation" information needed by regulators to accept the filing. ImClone said it would be able to answer the FDA questions by the end of the first quarter, leading, hopefully to an approval of Erbitux in the fall.

On January 4, 2002, the Cancer Letter published excerpts of the RTF letter indicating that—contrary to ImClone statements to investors—the FDA had a long list of concerns that went far beyond record keeping. The FDA believed ImClone's clinical trial was not adequate and well controlled and that additional studies would be needed. The letter suggested that the FDA had warned ImClone starting in August 2000 that its data would have to demonstrate that Irinotecan, the standard chemotherapy mentioned above, was needed along with Erbitux. But the data submitted by ImClone was not sufficient to distinguish the effects of the two treatments.

TRADING ACTIVITY BY IMCLONE EXECUTIVES AND OTHERS

Adding to the controversy over Erbitux has been the trading of ImClone stock by ImClone insiders a few weeks before the FDA letter, as well as the trading of stock by Waksal family relatives and friends during the 48 hours before the FDA letter was issued.

On December 21, 2001, ImClone issued a Company order stopping its employees from trading in ImClone stock until after the FDA decision on Erbitux was made public. Committee staff believes that no board member or officer of ImClone traded ImClone stock between December 21 and 28, 2001. However, staff found that, except for Sam and Harlan Waksal, members of Sam Waksal's immediate family sold ImClone stock on December 27, 2001 or the next day hours before ImClone announced publicly that FDA had refused to accept the filing of Erbitux.

We found that three officers of ImClone sold stock prior to December 18, 2001 on the advice of their broker. In addition, Harlan Waksal conducted a forward sale of 700,000 shares on December 6, 2001.

The staff learned that on October 31, 2001, Harlan Waksal notified the ImClone Board Members that he planned to execute a 700,000 share stock transaction. He told the board that the stock would still be under his voting control for the next three years. He also stated that he'd finalize transaction over the next two weeks. He told Committee staff that in early November 2001 he attempted to shop the sale. He told staff he was forced to sell the ImClone stock to come up with enough cash to pay substantial taxes racked up from his prior exercise of stock options and his tendering of shares to BMS. He also stated that because he didn't want to sell shares he entered into a forward sales contract that gives him a percentage of the cash value of the shares up front but still allows him to control the shares and defer tax payments for another two years. In short, Waksal received less than what the stock was worth at the time of the sale, but he also limited the downside risk when ImClone's stock price continued to drop. It should be noted that Harlan Waksal sold the 700,000 shares on the same day that ImClone hit its 52-week high.

This ends my prepared testimony, and I will be pleased to answer your questions.

Mr. GREENWOOD. Thank you, Mr. Papineau. The Chair recognizes himself for 5 minutes for questions, and let me address my questions to you, Dr. Weiss. You are a clinical professor of Medicine, is that right?

Mr. WEISS. Yes, sir. I am independent consultant in oncology.

Mr. GREENWOOD. Just pull that right up close to you, sir. Pull the microphone forward about 5, 6 inches.

Mr. WEISS. Does this work now? Yes.

Mr. GREENWOOD. Yes.

Mr. WEISS. Okay. I am a 100 percent self-employed independent consultant in oncology. I have a number of contracts with agencies of the Federal Government to do various tasks, and I am also a clinical professor of Medicine at Georgetown. That is an unpaid teaching faculty position.

Mr. GREENWOOD. Do you treat patients now?

Mr. WEISS. Yes, I do. I have an arrangement with an oncologist in solo practice who has offices on either side of the Maryland and Pennsylvania border in Gettysburg and Westminster, and I go to that office about 7 days a month to give him some time off and see patients, to maintain my clinical skills. I also have a contract with the Walter Reed Army Medical Center to go there 1 day a week to see patients in the breast disease clinic. So, yes, I do see patients, and I see patients with colon cancer too.

Mr. GREENWOOD. And for how many years have you audited scientific research?

Mr. WEISS. Yes. Since 1981, the National Cancer Institute has required onsite quality assurance auditing of the clinical trials that they fund at institutions around this country. There are 11 such cooperative groups, collaborating institutions, and I work for one of them, the Cancer and Leukemia Group B, which has its major grant handled by the University of Chicago, so I am a contractor to the University of Chicago for that grant. And I make site visits, as I did just the past 3 days, to institutions around the country, auditing the records, the medical records of patients that are in clinical trials.

Mr. GREENWOOD. Okay. And you reviewed the clinical trial data from Erbitux's 9923 study.

Mr. WEISS. Yes, I did.

Mr. GREENWOOD. Okay. In your report, you described as incredible the fact that 37 patients, almost 27 percent, of the 139 patients who were entered in that study were ineligible. Why is that percentage—why do you consider that percentage to be, quote, "incredible?"

Mr. WEISS. Because eligibility criteria for the clinical trial are most important. They determine the patient population you are going to study. They have to have the right cancer, they have to have the right stage, they have to have certain degree of normal liver function, normal kidney function, blood counts. All those sorts of things are criteria for being eligible to go on the study.

Mr. GREENWOOD. So in this study, there were only 139 patients that were entered, and 27 percent of them didn't meet the criteria for the study as it was designed.

Mr. WEISS. That is correct. That was determined by——

Mr. GREENWOOD. Is that an atypical rate?

Mr. WEISS. Yes, it is.

Mr. GREENWOOD. What it is a typical rate?

Mr. WEISS. To give you an example, just on Monday, one of the visits that I did, one of the 13 patients we audited was ineligible

for the trial. It was due to the mistake of the nurse data manager overlooking the fact the patient was still on a drug that made him ineligible. That is just pure human error. It happens 5, 6, 8 percent of the time. It doesn't happen 27 percent of the time.

Mr. GREENWOOD. Okay. And so what does you extrapolate from that with regard to the quality of the ImClone study?

Mr. WEISS. There are a lot of patients who were entered on the trial that did not meet the eligibility criteria as set up in the protocol, and therefore that automatically makes the results somewhat subject to question.

Mr. GREENWOOD. You also described as incredible the fact that 15 patients were exemptions to be enrolled in the study. What does that mean and why is that incredible?

Mr. WEISS. Once you set up these eligibility criteria, you do not deviate from them, except that you might make an error, as I just described. You don't give exemptions from these eligibility criteria, because if you do, then you have changed the patient population that you are studying. You have allowed on patients who weren't eligible for the study.

Mr. GREENWOOD. So is it highly unusual for exemptions to be given in such a study?

Mr. WEISS. Most certainly. In the Cancer and Leukemia Group B, with the 300 participating institutions, the only time an exemption can be given is by the group Chair at the University of Chicago. That means a phone call to the highest level, and that is rarely done, No. 1, make a phone call, No. 2, even more rare is to give the exemption.

Mr. GREENWOOD. Okay. I see in your report that you identified another set of major deviations in the study which involve the dose and the administration frequency of Irinotecan. Pronounce that for me.

Mr. WEISS. Irinotecan.

Mr. GREENWOOD. Irinotecan, the toxic chem. drug used in combination with Erbitux. How would the dosing and the frequency of dosing affect the results of the study?

Mr. WEISS. The protocol set up a standard for giving that particular drug and said that the dose and the frequency had to be the same as the patient received when they progressed; that is, their cancer got worse when they were on that drug previously. When they were treated on the protocol, I believe there were 17 patients did not get the same dose and same schedule of frequency of treatment as they were prior to entering. That is a major deviation.

Mr. GREENWOOD. How would you determine whether the patients were actually improving because of these drugs?

Mr. WEISS. You couldn't separate the effect of increasing the dose of the one drug from the effect of the combination of the two drugs, either the Erbitux and/or the Irinotecan. When you are giving more of one drug than you had before, you are changing the results, and, again, you make the results of the study subject to question.

Mr. GREENWOOD. The Chair's time has expired. The Chair recognizes the gentleman, Mr. Stupak, for inquiry for 5 minutes.

Mr. STUPAK. Thank you, Mr. Chairman.

Dr. Weiss, the patient eligibility, that was decided by who, the patient eligibility for these studies?

Mr. WEISS. They are set up in the protocol, and I assume the investigators entering the patient decided the patient met the eligibility criteria or not. But in the case of those 15 patients, they would have had to call somebody, perhaps at ImClone, I don't know, to say it is okay to handle that patient even though they are not eligible.

Mr. STUPAK. This study is known as 9923, correct?

Mr. WEISS. Yes, sir.

Mr. STUPAK. And the study was actually done in 1999, I believe.

Mr. WEISS. It was started in the end of 1999 and ended in early 2001.

Mr. STUPAK. And then after that August of 2000, ImClone and FDA met to see if they could get an accelerated approval of this drug, correct?

Mr. WEISS. Yes, sir.

Mr. STUPAK. Okay. After that meeting, there was a change in the protocol, was there not?

Mr. WEISS. Actually, the change in the protocol anti-dated that meeting by about 10 months. It was October 1999. And it is apparent, to me anyway, that the FDA staff did not know about the change in the protocol because their understanding was Version 1.0 of the study.

Mr. STUPAK. Correct. They thought it was Version 1.0, and in fact when the approval was given on Fast Track, which was, if I remember correctly, January 12, 2001, they were given the Fast Track authority to do protocol No. 1, correct?

Mr. WEISS. Yes, sir. That is what it appears.

Mr. STUPAK. In fact, even 7 days there later, FDA, on January 19, actually sent them a letter and talked about the first protocol, and that would be used in this Fast Track study.

Mr. WEISS. That is correct, sir.

Mr. STUPAK. Okay. If you go then to—let me back up just a little bit. While they were doing this study and everything, there has been a lot of discussion here about the July 30, 2001 Business Week article, and in the Business Week article, which was touting Erbitux, it stated that this drug was the furthest along of a handful of new cancer treatments that precisely honed in on a growth signal found in up to 50 percent of all cancers. In clinical trials, "the drug demonstrated remarkable success in causing colon cancer to regress in patients who had failed to respond to other treatments." Did you find in your review any medical evidence that the drug demonstrated remarkable success in causing colon cancer regression?

Mr. WEISS. No, sir. The patients who got a response, that is their cancer shrunk, the measurable lesions that were seen on a chest x-ray or a CT scan, the percentage that got that sort of response was in the 15 to 20 percent range. When you look at all of the people who have reviewed these CT scans and decided that they agreed, they agreed only on 20 patients and unfortunately there were all these disagreements, whether the patients truly were resistant to Irinotecan, No. 1——

Mr. STUPAK. Sure.

Mr. WEISS. [continuing] and, No. 2, whether they truly got a response to the protocol therapy.

Mr. STUPAK. Well, in your investigation, or Mr. Papineau, did either one of you find who was responsible for putting out the statement saying that you had remarkable success when at best the success was only 20 percent?

Mr. WEISS. It was Mr. Waksal is the one who did most of the touting of this drug.

Mr. STUPAK. Sure. Which Mr. Waksal was that?

Mr. WEISS. Mr. Sam Waksal.

Mr. STUPAK. Okay. Well, did you find in your investigation any evidence that, and I am going to quote again in a conversation that Mr. Waksal on the phone referenced as single agent data, "Apparently it came out at 13 percent, which he feels is half the C22-25, plus CUT 11 data. They have informed the FDA who were pleased and confirmed that they would be on for the February 28 FDA's Oncologic Drugs Advisory Committee," I take it the Advisory Committee for approval. Did you find anything, Mr. Papineau or Dr. Weiss, in which the FDA was, use the word, "pleased" and that there would be the expected February 28 that they would be on the Advisory Committee? Did you find anything like that?

Mr. PAPINEAU. We did not, sir. The FDA reviewers that we talked to were very clear that no statement like that was ever made to Sam Waksal.

Mr. STUPAK. Okay. Was it made to anyone else? If not Sam Waksal, was it made to anyone else that FDA was pleased with this single agent data?

Mr. PAPINEAU. Not that I am aware of, sir. There was talk about the single agent data and FDA wanted to see it. And ImClone told them that they had the data and they would present it to them at a later date. When it came time to present the data——

Mr. STUPAK. And, actually, that data wasn't submitted until late December, just before it was rejected.

Mr. PAPINEAU. It was finally given to them in total on December 4.

Mr. STUPAK. December 4. So whether it was the L.A. Times, business news, even statements about the remarkable success of this drug or FDA's apparently position with this drug, excitement about this drug, those are just—there is no basis of fact that you could find anywhere in your investigation to support those statements?

Mr. PAPINEAU. Not totally. What we did find from talking to the FDA officials is that they were listening to it and they couldn't talk because of the secrecy—the trade secrets and stuff of drug applications——

Mr. STUPAK. So during that time, even though they saw these statements publicly, they could not—FDA could not stand out publicly and say, "This is not true."

Mr. PAPINEAU. Exactly.

Mr. STUPAK. Because of the trade secrets and the ongoing study, correct?

Mr. PAPINEAU. That is exactly true. You will hear later from FDA witnesses. They will tell you that they watched "60 Minutes" and they read Business Week, and as they sat there and watched "60 Minutes" on Sunday night, they had a lot of problems in the

hype and what was being said, but there was nothing they could do about it.

Mr. GREENWOOD. Time of the gentleman has expired. The Chair recognizes the gentleman of the full committee, Mr. Tauzin, for 5 minutes for inquiry.

Chairman TAUZIN. Thank you, Mr. Chairman. Let me see if I can get all this in sort of layman's understanding. Our understanding from our investigation, gentlemen, is that this whole matter revolves around a mistake made in the early protocol that was based upon the notion that the way to test this drug, Erbitux, was to test it in combination with another toxic chemotherapy; is that correct?

Mr. WEISS. That is correct.

Chairman TAUZIN. And that mistake was based upon information that Erbitux alone didn't show enough effect, didn't show a reasonable amount of good results, that it had to be used in combination and tested in combination with other toxic chemotherapy; is that correct?

Mr. WEISS. Yes, sir. All drugs that go to clinical trials, whether they are cancer drugs or anything else, go through testing in animals. And when they tested this new drug, Erbitux, in animals, they found that they got the best results if they used Irinotecan and Erbitux together in the animal cancers.

Chairman TAUZIN. Yes. But, apparently, when the FDA medical reviewer handling this matter looked at it, the original decision was that the protocol shouldn't be approved. And then in August 11, the senior FDA medical official, in effect, overruled the primary review and said, "Yes, go forward with it," based upon this combination used; is that right?

Mr. WEISS. That is what it appears to be; yes, sir.

Chairman TAUZIN. And later on a single agent study indicated in fact Erbitux did have enough activity to indicate that it should have been studied by itself without studying it in combination with the toxic chem. you mentioned; is that correct.

Mr. WEISS. Yes, sir. A single agent study was subsequently done. Fifty-seven patients were entered and although six patients were said to have responded, the Bristol reviewers said they clearly agreed that five did respond. So that is about an 8 to 9 percent rate of regression of the cancer—number of patients who got benefit.

Chairman TAUZIN. Now, the 9923 study, which was the study that was used to approve the original protocol, apparently it had lots of problems. When BMS, Bristol-Myers Squibb, did the independent radiological review, they indicated that the response rate was only 12.5 percent compared to the claimed 22.5 percent. They found that the number of patients valuable under the system was 89 instead of the original 120. And if that data was correct, that would drop it below the 15 percent clinical end point set by ImClone, and the study would therefore be too small to support the accelerated approval process. So BMS, in its radiological review, ends up saying, "Hey, this process, 9923, this protocol that the FDA has approved, over the objections of the initial reviewer, is flawed;" is that right?

Mr. WEISS. Yes, sir.

Chairman TAUZIN. But they went ahead and invested anyhow and went ahead with that deal. Now, in the end, the end result of

all this was at some point, December something, FDA finally says, "This is not working. This review process is not doing its job, it is flawed, and so we are going to recommend a so-called refusal-to-file letter." Tell us what that is.

Mr. WEISS. That is basically a rejection——

Chairman TAUZIN. It is a rejection notice.

Mr. WEISS. It just says, "We are not going to review your study because there are too many problems with it."

Chairman TAUZIN. Now, you have been asked to independently review all this stuff, right?

Mr. WEISS. Yes, sir.

Chairman TAUZIN. The first question I want to ask you, if this drug is as important as it was hyped to be, was this a case—if ever there was a case that should have been handled absolutely carefully and correctly from Day One, wasn't this one?

Mr. WEISS. Yes, sir. Any time you have a study that is going to the FDA to get approval for marketing so that thousands of patients into the indefinite future get the drug, you want to be sure your scientific results and your study are iron clad.

Chairman TAUZIN. Yes, but more importantly, here is a drug that is being hyped as a blockbuster chemical treatment drug. Here is a drug that is being told it is going to revolutionize cancer treatment. Here is a drug that by all accounts is life or death for hundreds of patients who call in daily saying, "Get it to me."

Mr. WEISS. That is correct.

Chairman TAUZIN. Isn't this the kind of drug that should have been handled in the most careful, most precise, knowing ways so that FDA was assured from Day One that the protocols were correct, that everybody working with FDA, including Bristol Myers Squibb, everybody, should have been very careful that every T was crossed, every I was dotted, everything was done precisely right because of the importance of the potential of this drug to cancer therapy?

Mr. WEISS. Most assuredly.

Chairman TAUZIN. Now, you have looked at this process. Was there any doubt in your mind that it was flawed when you looked at it?

Mr. WEISS. The protocol had flaws in it.

Chairman TAUZIN. You could see it, couldn't you?

Mr. WEISS. Yes, sir.

Chairman TAUZIN. Why couldn't FDA? Why couldn't ImClone? Why couldn't Bristol-Myers see it? Why couldn't somebody see it early enough to say, "Stop. Let us stop it right now and start it up again correctly and do it right so that we don't delay this process the way it has now been delayed."

Mr. WEISS. I don't believe I can answer that question, sir.

Chairman TAUZIN. That is the question I think we have got to answer, Mr. Chairman. Thank you.

Mr. GREENWOOD. The Chair thanks the chairman and recognizes, for 5 minutes for inquiry, the gentlelady from Colorado, Ms. DeGette.

Ms. DEGETTE. Thank you, Mr. Chairman, and following up on Chairman Tauzin's question, the way the Fast Track process is supposed to work is if you have a promising drug, but you want

to move it more quickly because it is addressing some need that has not being addressed by existing drugs or it is being used on patients with no hope, Congress and the research community sort of said, "Well, we are not going to have the full-blown research Phase III studies that we might have with other drugs;" correct, Dr. Weiss?

Mr. WEISS. Yes, sir—yes, ma'am.

Ms. DEGETTE. I am used to it.

And so there is some sense with Fast Track approval that maybe you won't have the full-blown, years long research process, and that is accepted by everyone at the FDA, in the research community and by Congress.

Mr. WEISS. Yes.

Ms. DEGETTE. Okay. But nonetheless, the studies are supposed to have—are designed to have protocols which are acceptable scientifically, correct? I mean we don't abandoned scientific protocol simply because we want to get these drugs on the market, right?

Mr. WEISS. You not only have to have a scientifically valid protocol, but you have to have scientific valid patients and analysis of those patients that were entered on the study.

Ms. DEGETTE. And the problem with this—one of the problems with this study was that it was—it had a very small sample size to begin with. Am I correct in saying that?

Mr. WEISS. Relatively speaking, in clinical trials in cancer, yes.

Ms. DEGETTE. And it probably would have been all right as a stage two study, correct, Dr. Weiss, do you think?

Mr. WEISS. I am sorry?

Ms. DEGETTE. As a pivotal study, both of these protocols were undoubtedly flawed. We are getting all hung here about which protocol did the FDA know about, but as a study on which you would face Fast Track approval of a drug, both of these protocols probably had flaws, wouldn't you say?

Mr. WEISS. Yes. The major flaw was not requiring a specific dose and schedule of the Irinotecan. It was left up to the judgment of the physician, to some degree, by saying, "Give them the same dose and schedule that they had before."

Ms. DEGETTE. So if you were doing an FDA approval process, that study which didn't give any sense of the dose of the Irinotecan might have been all right as a preliminary study, but you would want to refine that study before you approved Erbitux for use in cancer patients, correct?

Mr. WEISS. Yes, and you would not ineligible patients on it either.

Ms. DEGETTE. Especially when you already had such a small sample size.

Mr. WEISS. Yes, most definitely.

Ms. DEGETTE. Okay. Now, was there any—do we have any idea why there was such a high percentage of ineligible patients in the protocol?

Mr. WEISS. I have no idea.

Ms. DEGETTE. So any answers would be speculative unless the researchers themselves could tell us, correct?

Mr. WEISS. They are speculative as far as I am concerned, I don't know.

Ms. DEGETTE. Okay. And I am a little curious about this discussion in August 2000 with the FDA and with ImClone where apparently the FDA was relying on an old protocol and ImClone had adopted a new protocol. Whose responsibility would it be to know that new protocol at that meeting? Would the be the FDA's responsibility or ImClone's responsibility?

Mr. WEISS. I would assume it is ImClone's responsibility to present it to the FDA and say, "Look, we have changed the study."

Ms. DEGETTE. Now, do we have—had ImClone, in fact, given that updated protocol to the FDA prior to the August 2000 meeting?

Mr. WEISS. I saw no evidence that they had.

Ms. DEGETTE. So you have no evidence that the FDA had that study in hand, whether or not they referred to it at the meeting or not.

Mr. WEISS. I do not.

Ms. DEGETTE. Okay. I just have a couple more quick questions. I have in my hand the report that you presented to this committee, Doctor. I assume you personally have overseen a number of protocols, given your background.

Mr. WEISS. Yes. I have personally participated in a number of clinical trials——

Ms. DEGETTE. Okay. Now——

Mr. WEISS. [continuing] written the protocols.

Ms. DEGETTE. On page 7 of your study, I don't know if you have it in front of you.

Mr. WEISS. Yes, I do.

Ms. DEGETTE. Okay. At the bottom, the very last paragraph, it says, "Flaws in the design of the 9923 protocol were also expressed publicly by three prominent medical oncologists after the publication of the RTF," which is the refusal-to-file letter. That was in January 2002 after everything fell apart, correct?

Mr. WEISS. Yes.

Ms. DEGETTE. I am wondering if you can tell me very briefly, because my time is up, what flaws those three prominent oncologists found in the protocols.

Mr. WEISS. The eligibility criteria regarding the patient being clearly resistant to the Irinotecan was one. The way that the specifications for giving the Irinotecan on this study, which I said were non-existent, those were the two major flaws.

Ms. DEGETTE. And are those flaws that should have been caught in the FDA Fast Track approval process?

Mr. WEISS. Yes, I believe they should have been.

Ms. DEGETTE. Thank you, Doctor. No further questions.

Mr. GREENWOOD. The time of the gentlelady has expired. The Chair recognizes the gentleman from Kentucky, Dr. Fletcher, for 5 minutes, for purposes of inquiry.

Mr. FLETCHER. Thank you, Mr. Chairman. Again, I want to thank you for conducting this hearing, and even though I had to step out briefly, I tried to listen to much of the testimony here.

Dr. Weiss, let me just ask you, in general terms, and I hope this hasn't been asked, but in spite of—if you look at the problems with the study, particularly eligibility, those that were entered into the study with lack of eligibility, some of the other things you pointed

out, does this drug, Erbitux, represent possibly a major breakthrough in cancer therapy, in your opinion?

Mr. WEISS. I would not describe it as a major breakthrough. I would describe it as an interesting drug with some activity apparent in colon cancer that makes it worthwhile to study further. We have many such drugs in the field of oncology.

Mr. FLETCHER. I certainly understand that and appreciate it. Let me——

Mr. WEISS. In other words, drugs that are interesting but not blockbusters.

Mr. FLETCHER. Thank you on that. And, obviously, we have heard much of the emphasis on the company management seemed to be on the financial dealings rather than making sure that the research was conducted adequately, and that does, at least—that appears from the testimony thus far and what we have heard occurred there.

Let me ask you this. It is very common for oncology agents to be used together because of the synergy. Sometimes they do not work alone, but they may work in combination with another medication. Help me understand why part of the refusal included making sure the drug was studied alone in efficacy alone. Doesn't the FDA sometimes permit to drug to use and say it is approved for use with another specific drug for a particular disease?

Mr. WEISS. Yes. This registration study involved the two drugs, and you want to be sure that one drug is really producing some additional benefit over the other drug when they are used together. And so you had no information that the new drug, Erbitux, all by itself provided any benefit. So when they are used together, you want to be sure that the new drug also has activity by itself along with the old drug, which you know has some activity. So if you see a response greater with the two, you know it is because, yes, the one drug works a little bit but the two work together better and higher percentage of patients benefit.

Mr. FLETCHER. Do the flaws in the study prohibit you even if statistically you rule out some of the problems due to the eligibility that the drug that Erbitux accompanied or was used with efficacy was not enhanced with Erbitux?

Mr. WEISS. It appeared to me that there was, for some patients, some benefit of Erbitux, both in the single agent study and in the combination study. The problem is with the combination study a large percentage of the patients were ineligible, many of them got doses higher of Irinotecan than they should have been, and there is a great deal of controversy over which patients responded and which didn't. So there are all sorts of flaws, and I don't think FDA could agree that it is a study that clearly makes a case for Erbitux as a drug that should be allowed on the market where anybody can prescribe it.

Mr. FLETCHER. Let me ask you then another question. Apparently, not only were there problems in following the protocol of the design of the study, but there were problems that you understand, and you may have already said this, problems in the design of the study itself then.

Mr. WEISS. Yes. The eligibility criteria for determining whether the patient was truly resistant to Irinotecan before they were en-

tered, that was a problem. And then the looseness—and I use that term as my own—the looseness of the directions on what dose of Irinotecan would be prescribed. It was stated that you give the same dose as they received before they went on study with no dose increase, but, obviously, the physicians involved went ahead and did that anyway. And that makes the results very suspect. Did the patient respond because they got the two drugs together or did they respond because they got more of the Irinotecan now than they did before.

Mr. FLETCHER. And I can certainly understand how that makes the results somewhat uninterpretable. Let me ask you, in this company you have substantial expertise on the board at ImClone, you have obviously substantial expertise in the FDA. How does this study, first off, get structured with these flaws, how does it get implemented with these flaws in conjunction with the FDA, and this allowed to go on? Could you help us with some insight on that?

Mr. WEISS. I can't answer that question, sir. One of the board of directors is somebody I used to work under at the National Cancer Institute, Dr. DeVita, whom I highly respect, and I don't know whether he actually saw the protocol or not.

Mr. FLETCHER. I find it, and the reason I do, certainly, many families, and I know our family's been affected personally with metastatic colon cancer, and I remember when the studies came out with 5-fu and Lamisil, we were very optimistic and it was apparently helpful, and we looked forward to this medication or others like this in not only metastatic colon cancer advance but other diseases. And if there is ever a time that you need to make sure for the timeliness of the availability of this drug that a study is done well, a study is conducted properly, that there is proper FDA oversight, that our Fast Track procedures were followed that were established by Congress, I mean this is the time you want it, because there is nothing more disheartening to raise the expectations of thousands of cancer patients that there is a new medication on the horizon and then to find out that it may still be, I mean it may still be a very good, effective medication, but the delay due to the flaws, and it looks like problems on both the companies and particularly with the FDA as well in overseeing the study, and maybe summon the process where a company can release and talk about how good this drug is and where the FDA, even if they have concerns, are prohibited, rightfully so, from talking about that. I would just like your discussion on what do you see can be done to prevent this in the future that we are not doing?

Mr. WEISS. I agree with you entirely that it was extremely unfortunate that the hopes of many patients with cancer were raised and somewhat dashed now by the fact that the study wasn't interpretable sufficiently to approve the drug for marketing. I honestly don't have an answer to the second part of your question, what can we do to change things. One of them is perhaps allow the FDA a little more latitude to make some of their analyses public. I think that is for Congress to decide, though.

Mr. FLETCHER. I see my time has expired, and thank you, Mr. Chairman.

Mr. GREENWOOD. The Chair thanks the gentleman. The Chair wishes to make one correction with regard to the testimony given

by Mr. Papineau. I believe you testified that the sale on December 6 by Harlan Waksal of stock occurred on the day of the highest value of the stock. I believe the record should be corrected that it was near—the highest day was December 5 and he sold on the 6th. I wish the record to be corrected. The Chair recognizes the gentleman from Florida, Mr. Stearns, for 5 minutes.

Mr. STEARNS. Thank you, Mr. Chairman. Dr. Weiss, did you see the "60 Minutes" CBS program on Erbitux?

Mr. WEISS. No, I did not.

Mr. STEARNS. Mr. Papineau, you did, and you——

Mr. PAPINEAU. No, I did not.

Mr. STEARNS. You did not. I think you indicated—staff told me that you thought that the executives Erbitux saw the "60 Minutes;" is that true?

Mr. PAPINEAU. I indicated that the FDA reviewers that were reviewing the drug watched "60 Minutes," and they——

Mr. STEARNS. Okay.

Mr. PAPINEAU. [continuing] had serious questions.

Mr. STEARNS. Okay. So the FDA people who reviewed the "60 Minutes" had serious questions?

Mr. PAPINEAU. Yes, sir.

Mr. STEARNS. Did the executives of ImClone, do you know if they saw the "60 Minutes?" Obviously, they did, but I mean it seems to me that if there were exaggerations in that "60 Minutes," somebody should have corrected the story.

Mr. WEISS. I would think so.

Mr. STEARNS. Now, that is not the FDA's responsibility.

Mr. PAPINEAU. No, it isn't. FDA is not allowed to do that.

Mr. STEARNS. Right. Dr. Weiss, who do you think should have the responsibility if there is a bad story from CBS, they have hyped this, in fact it appears on the July 30, 2001 issue of Business Week international cover story they were talking about what a great new cancer treatment drug this was. And it seems like the point I am getting at is all this hype in the media about this. Where did they get this hype from?

Mr. WEISS. It seems to be from the two executives that ran the company, the Waksal brothers.

Mr. STEARNS. Now, the Waksal brothers obviously didn't want to contact CBS "60 Minutes," and say, "No, you exaggerated," as CBS will say, "Well, this is what you told us." So you have these two brothers hyping this and then you have the media picking up and hyping it too.

Mr. WEISS. That seems to be the case; yes, sir.

Mr. STEARNS. So then the public is under the perception that it is legitimate because the media is promoting this, two legitimate media sources, "60 Minutes" and Business Week.

What does it mean when the FDA puts a drug on a Fast Track for an application?

Mr. WEISS. My understanding is that it is a drug that has a lot of interest, looks really hot and is one that should get on the market sooner rather than later, because it meets an unmet need for certain patients with cancer, and it works.

Mr. STEARNS. Does Erbitux legitimately make the argument for a Fast Track with FDA, and who makes that argument? Do the executives make it or does the FDA, and how is that determined?

Mr. WEISS. The executives make it. To some degree, the FDA has to accept it too.

Mr. STEARNS. And so the application was made by the executives and then the FDA approved it and put it on a Fast Track.

Mr. WEISS. That is my understanding.

Mr. STEARNS. And the evidence, the clinical evidence to put on a Fast Track has to be provided by ImClone, I guess, to the FDA and say, "This is what we have from our clinical evidence, and we expect it to be on a Fast Track."

Mr. WEISS. Yes, sir.

Mr. STEARNS. In your opinion, should drugs go on a Fast Track based on any new criteria or the criteria is satisfactory?

Mr. WEISS. Sir, they got a Fast Track by they first in the spring of 2000 came to FDA and asked for accelerated approval and Fast Track. They had that meeting that we have discussed in great detail in August of 2000. Part of that meeting was to decide whether or not it should be accelerated, and it was information that was made available to FDA at that meeting that FDA decided that they would give them accelerated—they would accelerate the application. In January of 2001, it was agreed it would go Fast Track. Fast Track simply means that as the application moves along, you can submit parts of it as you complete it. The actual application itself was presented to FDA on October 31, 2001. The biggest part of this Fast Track thing is that it gives the FDA 60 days to review it, which is what put the RTF letter into play.

Mr. STEARNS. Because it was on a Fast Track, it allowed the executives to submit documentation partially then; is that correct?

Mr. WEISS. Yes, sir.

Mr. STEARNS. Now, Dr. Weiss, you indicated the assessment of Erbitux based upon your available information. You said it is not a breakthrough drug, it is not a blockbuster drug, yet they got Fast Track. Describe the problems in the 9923 study—would you describe the problem in the 9923 study as merely missing documentation or much more serious?

Mr. WEISS. Much more serious. There are three major problems: One, a high rate of ineligibility; No. 2, that a large fraction of the patients were given different doses of the Irinotecan, major higher doses of the Irinotecan than they received before, which was against the protocol; and then, third, that there is a great deal of difference between the investigators, the ImClone Review Committee and the BMS consultants regarding who responded to the treatment and who did not; in other words, the cancer shrunk versus did not shrink. So those are the three major problems.

Mr. STEARNS. It seems to me that those are pretty transparent problems, that people who have a Ph.D. in immunology would know and should have gone ahead. I note that you discuss that ImClone attended the inclusion criteria of the 9923 study. What was this change and was it important?

Mr. WEISS. Yes. It changed the requirement of the amount of therapy the patient had to have with Irinotecan beforehand. In other words, the original version the patient had to have a signifi-

cant amount of that drug, 12 weeks of therapy and prove that their cancer grew despite that therapy. The protocol was changed that the patient could have had only a few doses, like on one patient as few as four. And that is 4 weeks of therapy, not 12 weeks. And you don't have sufficient information from just 4 weeks of therapy that the drug didn't work and the patient should now go on the study. That was the major change.

Mr. STEARNS. Thank you, Mr. Chairman.

Mr. GREENWOOD. The Chair thanks the gentleman and recognizes for 5 minutes the gentleman from North Carolina, Mr. Burr.

Mr. BURR. I thank the Chair. Dr. Weiss, you said that it was—the protocol was small and this was unusual. Is it unusual for a drug under Fast Track to have a small protocol?

Mr. WEISS. No, it is not. A hundred and twenty patients should be sufficient if you truly have reliable results and you really see a benefit of the treatment.

Mr. BURR. How many Fast Track processes have you testified on?

Mr. WEISS. I have never done this before.

Mr. BURR. And how many Fast Track processes have you reviewed as a medical professional?

Mr. WEISS. I have not had any experience at the FDA reviewing such things.

Mr. BURR. But you testify a lot because you are good. Is your consulting role to review things and potentially file a report on it?

Mr. WEISS. Yes. I both practice medical oncology, take care of patients, and I act in this role of quality assurance for the clinical trials that the National Cancer Institute supports.

Mr. BURR. How many Fast Track trials to date have used combination drugs in a Fast Track application?

Mr. WEISS. I have not reviewed any Fast Track applications, sir. I never worked for the FDA.

Mr. BURR. Yes, sir. I understand that, I am just trying to make sure the familiarity with the Fast Track process. But in fact this is the first time there has ever been a Fast Track process that used combination drugs. And in every case of the participants, they had to have already had a traditional chemotherapy approach that they had been non-responsive to; am I correct?

Mr. WEISS. Yes. I think that is true. I can't think of——

Mr. BURR. My understanding is that is true, and do we know in how many cases the particular drug——

Mr. WEISS. Irinotecan.

Mr. BURR. [continuing] Irinotecan was used?

Mr. WEISS. There is the original studies with that drug conducted back in the early to middle 1990's that allowed that drug to be approved for marketing.

Mr. BURR. And if I understand correctly from the notes I have got, Dr. Leonard Saltz, of the Memorial Sloan-Kettering Center, was intricately involved in the 9923 process?

Mr. WEISS. Yes. I know him and I hold him in high regard.

Mr. BURR. And what did he say when we interviewed him about these?

Mr. WEISS. I don't believe we did interview him, sir.

Mr. BURR. Oh, we didn't interview him, okay. And there were 27 clinical sites that participated in 9923 trial, am I correct?

Mr. WEISS. I am not sure. I would have to provide that for the record.

Mr. BURR. But it was a number of them. Did we talk to any of them relative to the discrepancies, the flaws——

Mr. WEISS. No, we didn't. We did not go out and interview any of the original investigators.

Mr. BURR. I am just trying to better understand—as a Member of Congress, and I may be the only one, I don't think I am, I get calls all the time from patients who have gone through the traditional mode and they have been non-responsive. And they pick up the phone and they call and they say, "Can you find a clinical trial? Can you get me in something?" I can sort of understand how people snuck into this. I am not sure who approved it, whether it was one of the clinical sites or whether it was somebody at the FDA, maybe somebody changed the guidance a little bit. Certainly, the numbers that you talk about that you found are disturbing, and I think they do, to some degree, question the results that were found. I think that it is real important that we understand better from those 27 clinical sites what transpired. How did we have the contamination of the pool? But I think to suggest that it was flawed because it was small is in fact because it was a Fast Track application, and I think that there is some degree of history to prove that that is the case usually when we have it.

Let me ask you, Dr. Weiss, if the pool of individuals who participated in this trial was clean, in other words the fit within the parameters, as you understand them, that were agreed to by the FDA and ImClone, would the results then, if they were the same percentages that you see today, increase or decrease your belief that there was something here that we ought to really pursue, as it relates to the colorectal cancer?

Mr. WEISS. It would increase it. The problems are, as I said, we don't know about the fact that there were so many ineligible patients, why that occurred. We know that some of the patients got a higher dose of Irinotecan than they should have, and we also know that there is a good deal of disparity between the various radiologists reviewing the CT scans to decide whether or not the patient got a response. But if everything were pure, then I can tell you it would be a very interesting drug. I don't know that I would call it a breakthrough, but it would be very interesting.

Mr. BURR. I purposely did not refer to it as a breakthrough and never try to on this committee to refer to anything as a breakthrough, other than when we actually pass a bill, because usually that is a breakthrough.

I think it is extremely important, though, that we understand better these 27 sites and why they made the decisions to either lower or raise the level of the chemotherapy drug that they were using in combination, because in fact by itself Erbitux showed some response but not tremendous response. It showed a much better response when used in combination with—what was the name of that chem. drug again?

Mr. WEISS. Irinotecan.

Mr. BURR. Irinotecan. But in the case of every person in the trial, they had gone through a traditional chemotherapy approach and had been non-responsive; in other words, their problem had not

gotten better. In most cases, it had gotten worse; at best, it had stayed the same, am I correct?

Mr. WEISS. Yes.

Mr. BURR. So there was some promise that was there. Mr. Chairman, I know my time has run out, and I hope that either in other information that we have from our staff report or from other witnesses we can better understand these discrepancies that deal with the makeup of the protocols, why there were deviations in the size of the chemotherapy that was given, and hopefully we can follow up with Dr. Saltz and the 27 sites.

Mr. GREENWOOD. The Chair thanks the gentleman. Just to clear the record, Dr. Weiss, you did review some of the audit reports from some of the 27 sites; is that correct?

Mr. WEISS. Yes, sir.

Mr. GREENWOOD. Okay. The Chair thanks—Dr. Fletcher asks unanimous consent for an additional 2 minutes for purpose of inquiry.

Mr. FLETCHER. Thank you, Mr. Chairman. I just had one more question, especially the gentleman from North Carolina certainly spurred my interest in the fact that looking at Bristol-Myers Squibb, which purchased this company and I think still, obviously, has a belief that this medication will help in colorectal cancer, metastatic colorectal cancer, especially in patients who have had failed conventional therapy. I mean this is a company that invested a substantial amount of money. They have a tremendous amount of expertise in this area. They looked at this study. Now why do you think in looking at this study that they still believe that this medication certainly has a great deal of viability and yet you seem to dismiss the study substantially?

Mr. WEISS. I do not dismiss the study substantially. I say there are so many problems it is hard to know whether the drug really works. And I do not know why the BMS people went ahead with it, but I guess that I could use the analogy they thought they were getting a diamond and they turned out to have gotten a zircon.

Mr. FLETCHER. Let me ask you just one follow-up with that, and that is that what are the side effects of this medication?

Mr. WEISS. It has two side effects. One is any time you give a protein, which it is, to anybody there is always the chance of allergy.

Mr. FLETCHER. Percentage of that, do you have it?

Mr. WEISS. Three or 4 percent. And the patient can't get any more of that drug because they are allergic to it. The other major side effect——

Mr. FLETCHER. Does that include any anaphylactic reaction or life-threatening——

Mr. WEISS. Yes. That is exactly what I mean. And the other major side effect, where 85, 90 percent of the patients get it, is they get cases of acne, skin reaction, and sometimes it is bad enough so the patient wants to stop the therapy.

Mr. FLETCHER. Thank you very much. Thank you, Mr. Chairman.

Mr. GREENWOOD. The Chair thanks the gentleman. The Chair wishes, without objection, to enter two documents into the record. One is the staff report entitled, "An Inquiry into the ImClone Cancer-drug Matter, Preliminary Committee Staff Report," and the sec-

ond is a report to the House Committee on Energy and Commerce by Dr. Weiss. Without objection, those documents will be entered into the record.

[The reports follow:]

AN INQUIRY INTO THE IMCLONE CANCER-DRUG MATTER

PRELIMINARY COMMITTEE STAFF REPORT

At the direction of Chairman W.J. "Billy" Tauzin and Subcommittee Chairman James C. Greenwood (later joined by Ranking Minority Member John D. Dingell and Subcommittee Ranking Minority Member Peter Deutsch), Committee staff conducted an investigation into matters surrounding the development by ImClone Systems, Inc., (ImClone) of its colorectal cancer drug Erbitux (also known as C225 or Cetuximab).

ImClone, a small biotechnology company based in New York, was founded by two brothers, Drs. Sam and Harlan Waksal, in 1984. ImClone developed a cancer therapy drug called Erbitux, reportedly spending more than $200 million on research on this drug. ImClone has never turned a profit in its 18 years of existence.

In the spring of 2000, ImClone sought accelerated approval from the Food and Drug Administration (FDA) to market Erbitux to meet the medical need of colorectal cancer patients who have failed to respond to standard chemotherapies. ImClone and Erbitux are internationally known, having been featured on the CBS news program "60 Minutes," and the international cover of the July 30, 2001 issue of *Business Week*. One reason Erbitux received such attention is that, according to *Business Week,* this drug was "the furthest along of a handful of new cancer treatments that precisely home in on a growth signal found in up to 50% of all cancer types." In clinical trials, "the drug demonstrated remarkable success in causing colon cancer to regress in patients who had failed to respond to all other treatments." Erbitux also is promising because it is an antibody that targets and blocks off cancer cells, without the high degree of side effects from standard cancer treatment. Such promise apparently prompted thousands of cancer patients to try to obtain Erbitux either through clinical trial enrollment or "compassionate use" access. For example, *USA Today* reported that ImClone had received 400 calls a day from patients desperate to get Erbitux outside of clinical trials

In September 2001, Bristol-Myers Squibb (BMS) bought 19.9 percent of ImClone for $1 billion, and agreed to pay as much as $1 billion more to obtain the marketing rights to Erbitux. On October 30, 2001, ImClone submitted its Biologics License Application (BLA) for Erbitux to FDA. On December 17, 2001, ImClone was one of seven biotechnology companies included for the first time in the NASDAQ 100 index. Excitement and confidence in ImClone was reflected in such media reports as an article in the December 26, 2001 *Los Angeles Times,* which proclaimed, "Erbitux, a colon cancer treatment from ImClone Systems Inc., is set to make one of the biggest splashes of 2002."

Many observers and investors were thus stunned to learn that, on December 28, 2001, FDA issued a "refuse-to-file" (RTF) letter in response to the ImClone license submission. The RTF letter is sent in rare cases when a submission is deemed insufficient, and is a non-public document, since it contains trade secret or confidential commercial information. ImClone publicly announced the FDA decision the evening of December 28th, which prompted a sharp sell off in ImClone shares starting on December 31, 2001.

The Committee's investigation focused on the validity of the claims that were asserted about ImClone's effectiveness, the FDA filing and review process, and evidence uncovered by the Committee that friends and family members of ImClone's founders sold large amounts of ImClone stock just prior to ImClone's receipt of the negative determination from FDA.

METHODOLOGY

To review the above issues, Committee staff conducted hundreds of hours of interviews with officials from ImClone, BMS, and other pharmaceutical companies, FDA, Wall Street firms, patient advocacy groups, oncologists, and representatives of family and friends of Sam and Harlan Waksal. Staff also obtained and reviewed thousands of documents from the above officials, corporations, and FDA. These documents and discussions with officials included, but were not limited to, the FDA drug approval process, clinical trials, the BMS tender offer and milestone payments with ImClone, events leading up to the FDA refusal-to-file letter, stock trading by ImClone officials and Waksal family and friends, and ImClone's filings with the Se-

curities and Exchange Commission (SEC). Staff also reviewed the due diligence activities conducted by seven other major pharmaceutical firms during 1999 and 2000, to determine what they learned about ImClone and its products, and what their rationale was for not entering into an alliance with ImClone, as BMS did in 2001.

THE FDA PROCESS: ACCELERATED APPROVAL AND FAST-TRACK DESIGNATION

The ImClone case highlights the policy question of how to test cancer drugs in a way that balances rapid access to life-saving drugs with the need to ensure that the drugs work, particularly when a publicly traded company is involved. In the standard approval process for a drug, FDA normally requires one or more large clinical trials (usually called Phase III trials) showing that a drug prolongs life compared with a placebo or with an already-approved drug. Such trials can take years, involve thousands of patients, and cost hundreds of millions of dollars to perform.

When a company develops a drug for patients with life-threatening diseases and there are comparatively few treatment options available, FDA sometimes approves the new drug based on smaller trials, without a control group for comparison. The trials normally look at whether tumors are shrinking, which can be determined much faster than whether patients are living longer. Often, these trials are limited to patients who have not responded to existing therapies (known in medical terms as "refractory" patients). If FDA approves a drug based on such small trials, it typically requires companies to conduct additional studies to show more widespread benefit, such as additional survival time.

In ImClone's case, the company was trying to get approval for Erbitux based on a study where the drug was used in combination with an approved chemotherapy, in a universe of approximately 120 patients—a very small patient pool. ImClone's strategy appears to have been unprecedented. According to the BMS Due Diligence Findings, dated June 12, 2001: "No accelerated approval has ever been granted for an oncology drug for use in a combination therapy." It also should be noted that ImClone was seeking FDA's agreement for accelerated approval with a protocol design of a study that already had been conducted.[1]

The Committee's investigation focused on two areas of the FDA process prior to the submission of ImClone's BLA for Erbitux in October 2001: (1) the clinical protocol design and conduct of the pivotal 9923 study, and (2) the single-agent study of Erbitux.

In the spring of 2000, ImClone had two Phase II clinical trials that looked promising for accelerated approval: a study in head-and-neck patients, and a study in colorectal cancer patients. ImClone originally anticipated that it would be the head-and-neck trial that would be the vehicle for possible FDA approval. However, because of faster accrual of patients and promising results, it was the colorectal cancer patient study, known as the 9923 study, that ultimately formed the clinical core of ImClone's BLA. According to ImClone, the results of the 9923 study showed a 22.5% positive response rate in colorectal cancer patients who already failed the standard chemotherapies.

In August 2000, ImClone was scheduled to meet with FDA to discuss, among other things, whether the results of the 9923 study were clinically meaningful and whether 9923 could meet accelerated approval criteria and receive fast-track designation. Prior to the ImClone meeting, FDA officials held an internal "pre-meeting" to prepare. At this pre-meeting, the primary FDA medical review officer indicated her reservations concerning the 9923 study. Her notes from this meeting state: "1) Is ORR [overall response rate] = 15% clinically meaningful for colorectal CPT-11 failure? Only if as a single agent. 2) CP02-9923 meet accel. approval criteria and fast track? *No*." According to Committee staff interviews, nobody on the FDA staff expressed disagreement with the assessment of the medical review officer at this internal "pre-meeting."

On August 11, 2000, FDA met with ImClone officials and consultants to discuss ImClone's accelerated approval strategy using the 9923 study. According to the minutes of this meeting prepared by FDA, FDA participants described the 9923 study during this meeting as follows:

> "This is a Phase 2 open label study of Cetuximab [Erbitux] plus irinotecan in metastatic or recurrent colorectal cancer refractory to irinotecan. Following two courses of irinotecan, patients' tumors are measured and based on the re-

[1] Some companies meet with FDA before they conduct the clinical trial to seek the agency's input and guidance on the clinical protocol design. Agreements between the company and FDA can be made binding through Special Protocol Assessments. Although FDA's Center for Drugs has used dozens of these assessments for cancer drugs, the FDA's Center for Biologics (the division handling ImClone) had never used one for a biologic product, other than in one instance involving a vaccine.

sults, divided into the Stable Disease Treatment Group (tumor volume change < 25%) or the Progressive Disease Treatment Group (tumor > increased in volume 25%). Patients then receive irinotecan plus cetuximab until treatment failure."

This description accurately tracks the first version of ImClone's protocol for 9923. According to that August 2, 1999 Version 1.0 of Protocol IMCL CP02-9923, Section 3.1.2, the patient "must have demonstrated progression of disease after completing a minimum of two courses of a regimen containing irinotecan." However, a few months later, when patients were being enrolled into the study, ImClone relaxed the inclusion criteria in an amended protocol. According to the October 18, 1999 Version 2.0 of Protocol IMCL CP02-9923 amended Section 3.1.2 (Inclusion Criteria), the patient "has documented stable disease (must have received a minimum of 12 weeks of irinotecan therapy) or *progressive disease at any time after receiving an irinotecan-containing regimen.* Copies of scans must be provided to confirm the lack of an objective response to prior therapy." (Emphasis added).

Therefore, FDA was relying on an outdated version of the protocol at the August 2000 meeting with ImClone. Yet nobody from ImClone informed FDA about the amended protocol at this meeting or any time thereafter. Moreover, the minutes of the meeting taken by the company and FDA were exchanged, yet, again, the company did not correct the FDA's misunderstanding on this point.

At the August 11, 2000 meeting with ImClone, the most senior FDA medical officer agreed that "the basic trial design is probably acceptable,"—albeit, relying on the incorrect version of the study protocol—and, in effect, overruled the view of the primary medical reviewer that had been expressed at the pre-meeting among FDA personnel. The senior FDA officer told Committee staff that her decision to accept the protocol was based on her belief that she should be flexible for a promising drug meeting an unmet medical need, but was also based on representations that ImClone made about the special synergistic effect of Erbitux when used in combination with irinotecan. The senior FDA officer said that ImClone asserted that Erbitux showed no activity when used alone, which would support the claim of synergistic effect. This assertion was based on animal data and one small human trial. In the context that ImClone discussed this point, she assumed the human trial involved human colorectal cancer patients. The senior FDA officer later learned that the human trial involved renal cancer patients, which cannot be used as a basis for determining single-agent activity in colorectal cancer patients. ImClone disputes that the issue of single-agent activity came up at the August 11, 2000 meeting, but the company agrees that the issue was discussed in subsequent phone calls and meetings with FDA.

On January 12, 2001, FDA granted fast-track designation for Erbitux. The FDA fast-track designation appears to be based on the inclusion criteria of the outdated version of the 9923 protocol. According to the January 12, 2001 letter to Nikhil Mehta of ImClone from Glen Jones of FDA: "[W]e are designating as a Fast Track development program the investigation of cetuximab in combination with irinotecan for its effect on durable tumor responses (complete and partial responses) in patients with metastatic colon cancer who are refractory to standard chemotherapy (5 fluorouracil and irinotecan), *where refractory is defined as progressive disease during at least two cycles of standard doses of 5-fluorouracil and irinotecan."* (Emphasis added).

On January 19, 2001, FDA sent a letter to ImClone requiring them to conduct a small study of 25-50 patients to test the response rate when using Erbitux alone as opposed to being used in combination with the toxic Irinotecan. As FDA explained:

> "You are expected to study and submit the following in order to have a biologics license application which meets filling criteria and in order for your development program to continue to meet the criteria for Fast Track designation:
>
> 1. Preclinical and clinical data (including at least 25-50 patients) which excludes the possibility (e.g., through establishment of the upper limit of the 95% confidence interval around the observed response rate and the lower limit of the 95% confidence interval around the observed response rate with combination therapy) that the response rate observed with the combination of irinotecan and Cetuximab [Erbitux] would not be observed with single agent Cetuximab at the dose and schedule proposed. You must provide evidence that continuation of a toxic agent (irinotecan) is necessary to achieve the desired clinical effect. If you do not have such data, you should generate this information in a randomized controlled trial directly comparing the efficacy of single agent Cetuximab (the generic name for Erbitux) to the combination of Cetuximab plus irinotecan to establish the contribution of irinotecan in this setting."

During the winter and spring of 2001, while conducting the single-agent study, ImClone was actively pursuing a joint venture or a sale of the company, or of a majority interest in the company, to several pharmaceutical companies. It appears that, in pursuing such an arrangement, the ImClone leadership attempted to downplay the significance of the single-agent study required by FDA. For example, according to one drug company official's e-mail, dated April 6, 2001:

> "They [Imclone] have to complete the pilot trial of C225 [Erbitux] alone in refractory colon cancer patients, 25-40 patients. The FDA has required a final study report from this trial prior to an ODAC [Oncologic Drug Advisory Committee] meeting. Per [ImClone] estimately [sic], they believe a final study report will be sent Oct/Nov, meaning a likely Spring ODAC meeting. According to Harlen [reference to Harlan Waksal], the FDA has agreed that while this study is necessary for filing, it will not impact the approval of the combination in refractory. They need to have the single agent activity per their regulations. They won't use the small trial to compare RR [response rate] of the single agent to the combo, but will use it to help plan further development of C225 as a single agent if appropriate."

On October 12, 2001, ImClone finished its single-agent study. The results of this study showed six responses out of 57 patients, for a response rate of 10.5%. As FDA noted in its December 28, 2001 refusal-to-file letter: "Based on the summary information provided, and assuming that the results can be confirmed, the data do not show that the response rate observed with the combination of Cetuximab and irinotecan could not also be observed with single agent Cetuximab at the dose and schedule proposed."

Even though there was a difference in the response rates (10.5% single agent; 22.5% combination), because both studies had such small populations, the confidence intervals overlapped and, thus, there was still a possibility that a very sick colorectal cancer patient could respond just as well with Erbitux alone as with Erbitux combined with a toxic chemotherapy. As a result, additional studies would be needed to isolate and establish the contributions of each drug. These additional studies would, at a minimum, significantly delay the launch of Erbitux.

However, it appears that ImClone attempted to portray the results of the single-agent study and the prospects for its application in an inaccurate light to BMS, its likely new business partner. According to an October 12, 2001 e-mail from BMS Chief Scientific Officer Peter Ringrose to other BMS executives: "I just had Sam Waksal on the phone re the single-agent data. Apparently it came out at 13% which he feels is half the C225 plus CPT-11 data. They have informed the FDA who were "pleased" and confirmed that they would be on for the Feb 28 ODAC (FDA's Oncologic Drugs Advisory Committee). He reckons they will be on the market by March. I am planning to meet with Sam in NY week after next."

But, according to Committee staff interviews with FDA personnel, no one at FDA spoke to ImClone about the single-agent data on or around October 12, 2001, and FDA had never placed Erbitux on the agenda for the February 2002 ODAC meeting. The submission of the single-agent study to FDA was not completed until December 4, 2001.

To more closely evaluate these two studies relied upon by ImClone, the Committee hired an expert consultant to review the studies' designs, protocols, and results. The key findings from this review are contained in a Report to the House Committee on Energy and Commerce by Raymond Weiss, MD, FACP (attached as an appendix to this report).

THE FILING OF THE ERBITUX APPLICATION AND FDA'S REVIEW

On October 31, 2001, ImClone completed its BLA application for Erbitux by submitting the clinical portion of the BLA to FDA. This clinical portion included the records for the 9923 study and the single-agent study 0141 (except for data on 17 patients, which was submitted on December 4, 2001). Under the fast-track designation of the FDA Modernization Act of 1997, the agency was required to complete its review of Erbitux and determine filability within 60 days of the submission date. Until this submission, FDA had relied on assurances from ImClone and the records in ImClone's Investigative New Drug file. FDA did not actually see the details of the clinical trials for Erbitux until ImClone submitted this portion of its BLA at the end of October 2001. Upon reviewing the clinical portion, FDA reviewers immediately identified significant problems, and the number of problems continued to mount as their review continued in November 2001. According to the FDA reviewers, the Erbitux application, as filed, raised serious questions and lacked needed information that ImClone had been advised on several occasions would be required as part of the application. The FDA reviewers told Committee staff that it was read-

ily apparent that the clinical research was severely deficient and could not meet the legal requirement of an adequate and well-controlled clinical trial.

On November 30, 2001, key FDA reviewers reached the conclusion that problems in the clinical portion were so severe that there was no option but to issue a refusal-to-file (RTF) letter, a rare event. On December 4, 2001, after raising the prospect of an RTF in a conversation with one of the FDA reviewers, ImClone's Regulatory Affairs Vice President formed an impression for the first time that an RTF letter was a realistic possibility, according to her interview with Committee staff. That same day, she reported this conversation and FDA's concerns to Dr. Harlan Waksal. On December 5, 2001, FDA management decided ImClone would receive an RTF letter. On December 7, 2001, a BMS Regulatory Affairs executive reported that she was not sure ImClone fully understood the implications of the comments of a FDA medical reviewer regarding the individual contributions of the drugs in the combination trial. In the e-mail opinion of the BMS executive, based on the FDA reviewer comments, "a refusal to file decision doesn't appear altogether unlikely at this point."

Both FDA and officials from the two companies told Committee staff that the tone of conversations between the agency and ImClone dramatically changed following the early December discussions with FDA. By mid-December 2001, it was clear to both ImClone and BMS that FDA had serious concerns about the Erbitux drug application. After a teleconference with FDA on December 12, 2001, key ImClone executives perceived an increased probability of an RTF letter, according to their interviews with Committee staff. On December 20, 2001, FDA told ImClone and BMS to no longer contact the agency until after they received FDA's letter on filability on December 28, 2001. Some personnel from ImClone and BMS thought from the tone of this conversation that an RTF letter was likely, but some in ImClone still held out hope for a positive FDA response. On December 24, 2001, an outside consultant for BMS was able to get an incidental confirmation from a source at FDA that FDA would be sending an RTF letter to ImClone. The next day, December 25, BMS Senior Vice President for Marketing Brian Markison called Dr. Harlan Waksal, who was vacationing in Colorado, to inform him of this confirmation BMS' consultant had received from an FDA source. Dr. Sam Waksal was vacationing at a Caribbean island and returned to New York on December 26, 2001.

It appears that Sam and Harlan Waksal and other key ImClone and BMS executives knew about the RTF letter by the morning of December 26, 2001. That day, ImClone sent a letter to FDA in an attempt to prevent the RTF by offering to waive its rights to the 60-day deadline that FDA had to meet by December 28, 2001. FDA declined the offer on the grounds that ImClone could not legally waive the deadline. On December 27, 2001, Sam Waksal for the first time personally interacted with FDA with respect to Erbitux, calling a senior official at FDA's Center for Biologics he knew when Waksal worked at the National Institutes of Health. The purpose of this call appears clear. Based on internal notes produced to the Committee by ImClone, dated 12:00 noon on December 27, 2001, "Sam and Harlan [Waksal] are calling FDA to try to stop RTF." The senior FDA official declined to intercede, and on December 28, 2001, at approximately 2:55 p.m., FDA faxed the RTF letter to ImClone. The company in turn publicly revealed the receipt of the letter later that day, at approximately 7:14 p.m.

THE RTF LETTER AND SUBSEQUENT EVENTS

As discussed above, on December 28, 2001, FDA issued a refusal-to-file letter in response to the ImClone submission. The RTF letter, sent in rare cases when a submission is deemed insufficient, is a non-public document containing trade secret or confidential commercial information. In its December 31, 2001 investors' conference call, ImClone executives said that FDA regulators sent the RTF letter because the Erbitux application was missing certain "train of documentation" information needed by regulators to accept the filing. ImClone said it would be able to answer FDA's questions by the end of the first quarter, leading, hopefully to an approval of Erbitux in the fall of 2002. On the first trading day after the issuance of the RTF letter, ImClone's shares fell $11.15, or 20 percent, to $44.10 per share.

On January 4, 2002, the *Cancer Letter* published excerpts of the RTF letter, which indicated that FDA had greater concerns about ImClone's data than company executives stated in the December 31 conference call with analysts and investors. The Cancer Letter article reported that the RTF letter detailed a long list of FDA concerns that went far beyond record keeping. The FDA was quoted as saying that ImClone's clinical trial was "not adequate and well controlled," and that additional studies would be needed. Moreover, the letter suggested that FDA had warned ImClone starting in August 2000 that its data would have to demonstrate that

irinotecan, a standard chemotherapy, was needed along with Erbitux. But the data submitted by ImClone was not sufficient to distinguish the effects of irinotecan and Erbitux. After the Cancer Letter report appeared, ImClone shares fell sharply further, to open on January 7, 2002, at $34.96 per share.

On January 9, 2002, after ImClone had lost nearly $1.5 billion in market value since December 28, 2001, and after the filing of at least 11 federal class action lawsuits, Sam Waksal, ImClone's president and chief executive officer, attempted to explain the company's situation at the J.P. Morgan H&Q Healthcare conference. "What happened was that we put together a faulty package and we screwed up," Waksal reportedly said. The principal problem, he said, was the company's failure to provide documentation demonstrating that the patients enrolled in ImClone's pivotal trial had met the eligibility criteria.

THE BMS-IMCLONE PARTNERSHIP AND IMCLONE'S LOANS TO KEY OFFICIALS

During 1999 and 2000, ImClone invited BMS, as well as several other major pharmaceutical firms, to meet with representatives of ImClone to conduct due diligence with a view toward acquiring a majority ownership in ImClone. Over this time period, several pharmaceutical firms, including BMS, met with Sam Waksal and conducted preliminary due diligence activities. Each pharmaceutical firm, including BMS, concluded that the price being asked by ImClone was too high to continue discussions at that time.

In early 2001, BMS conducted an extensive internal review of its own biologics business, and evaluated a number of opportunities to expand its biologics capabilities. BMS concluded in April 2001 that ImClone's IMC-C225 compound, Erbitux, could sustain its leadership position in oncology, significantly contribute to its corporate growth strategy, and provide a significant step towards BMS becoming a leader in biologics.

In mid-April 2001, Mr. Brian Markison, BMS Senior Vice President of Marketing, contacted Dr. Sam Waksal to determine whether ImClone would be interested in pursuing a deal involving a significant equity investment in ImClone by BMS. On May 3, 2001, Dr. Waksal, Mr. Markison and Dr. Peter Ringrose, Chief Scientific Officer of BMS, met in New York City to discuss BMS' interest in ImClone. During that meeting, Dr. Waksal outlined the type of deal that would be acceptable to ImClone. Dr. Waksal's preference was that ImClone remain a publicly traded entity after the deal. As a result, Mr. Markison agreed to explore a possible transaction whereby BMS would acquire a majority interest of ImClone in return for BMS common stock, together with a separate agreement providing for the commercial rights to IMC-C225 by BMS.

After further discussions, on May 19, 2001, the two companies entered into a confidentiality agreement, and BMS conducted further due diligence of ImClone. On June 1, 2001, Mr. Richard Lane, President of BMS' Worldwide Pharmaceutical Division, and Dr. Waksal met to discuss an outline of a deal prepared by ImClone's legal advisors that called for an acquisition by BMS of a 70% stake in ImClone.

On June 5, 2001, BMS' Board of Directors entertained the majority ownership deal with ImClone. However, some BMS board members raised concerns about acquiring majority ownership of ImClone, and suggested that BMS seek an arrangement of less equity in ImClone while still securing the rights to C-225. On June 7, 2001, representatives of the two companies met to discuss BMS' proposed due diligence activities. Shortly thereafter, employees of BMS and representatives of its legal and financial advisors conducted an extensive due diligence review of ImClone in the areas of clinical development, legal matters, information technology, marketing and sales, tax, finance, manufacturing, intellectual property and regulatory affairs.

In late June 2001, BMS concluded that the acquisition of a minority interest in ImClone, together with a separate commercial agreement relating to the co-development, co-promotion, and distribution of ImClone's IMC-C225 compound, would be a preferable structure for a deal with ImClone. Thereafter, Dr. Waksal was contacted by Mr. Peter Dolan, Chief Executive Officer of BMS, and Mr. Lane, who confirmed to Dr. Waksal that BMS no longer had interest in a deal to acquire a majority interest in ImClone where ImClone remained a publicly-traded entity. Mr. Dolan and Mr. Lane reaffirmed BMS' interest in ImClone and BMS' intent to consider other deals that met the economic and business objectives of both companies. Dr. Waksal stated that he was willing to consider alternative proposals, but emphasized that he was not interested in a commercial transaction that did not also include a significant equity investment in ImClone by BMS. Dr. Waksal also advised BMS that he felt ImClone's existing stockholders would benefit most if BMS acquired an equity interest through a tender offer to ImClone's existing stockholders.

On June 26, 2001, BMS provided ImClone with an outline of a proposed commercial transaction for the co-development, co-promotion, and distribution of IMC-C225, and an equity structure that proposed an acquisition of a 19.9% interest in ImClone by BMS. During the end of June and the first two weeks of July 2001, BMS and ImClone, and their respective legal and financial advisors, met several times to discuss terms and conditions of a 19.9% equity investment and a commercial transaction relating to rights to IMC-C225. Also during this time, the two companies and their respective financial advisors discussed the price at which BMS would offer to purchase the ImClone shares, which would be at a significant premium to the publicly-traded stock price.

In mid-July 2001—after ImClone was virtually assured of the 19.9% equity deal and in anticipation of the lucrative tender offer from BMS—ImClone's Board of Directors agreed to lend $35 million to Sam and Harlan Waksal and Robert Goldhammer, the Chairman of the Board, to provide them with an opportunity to exercise stock options and warrants they held to purchase a total of approximately 4.5 million shares of ImClone stock. Sam Waksal and Harlan Waksal's loans were $18.2 million and $15.7 million respectively. Mr. Goldhammer's loan was in the amount of $1.2 million. These unsecured loans were at an interest rate equal to the prime lending rate plus 1 percent (7.75 percent on the date of the note).

On July 20, 2001, BMS and ImClone agreed, on a preliminary basis, to a tender offer price of $70.00 per share. On September 17, 2001, the Board of Directors of BMS unanimously approved the ImClone deal. On September 19, 2001, ImClone's Board of Directors approved the deal, and both companies issued separate press releases announcing that BMS would acquire 14.4 million shares, or about a 20 percent stake, of ImClone's common stock for $1 billion through a tender offer of $70 a share, exclusively set aside for ImClone shareholders. At the time of the announcement, ImClone shares were selling at roughly $40 per share. BMS also agreed to pay as much as another $1 billion in milestone payments in return for the marketing rights to Erbitux in the United States.

On October 29, 2001, thousands of ImClone's shareholders participated in the BMS tender offer to purchase ImClone stock at $70 a share, a $20 premium over the increased trading price. Sam Waksal sold 814,674 shares, and Harlan Waksal sold 776,450 shares, or just more than 20% of each of their holdings. Although all ImClone shareholders were allowed to tender their shares of ImClone stock to BMS, only the Waksals, the Chairman of the Board, and one other board member were given loans by ImClone to purchase ImClone stock, at highly discounted prices, and then tender it to BMS at $70 per share.

A number of experts in the financial and biotech areas told Committee staff that there is no precedent in pharmaceutical-biotech alliances for the BMS and ImClone deal, which resulted in the immediate personal enrichment of top executives through a tender offer to existing shareholders. The more typical alliance formed between a major pharmaceutical company and a smaller biotech firm is centered on milestone payments that provide much needed cash to the biotech firm.

BRISTOL-MYERS SQUIBB DUE DILIGENCE OF IMCLONE

The Committee's investigation also focused on BMS' due diligence into the clinical research behind Erbitux prior to its decision to strike a commercial deal with ImClone. In May 2001, BMS scientists were mobilized to examine the clinical research package. On June 14, 2001, BMS Senior Vice President Laurie Smaldone sent an e-mail to her colleagues Peter Ringrose and Beth Seidenberg concerning ImClone, stating: "On the whole this remains a very high risk opportunity." Among the critical outstanding issues she cited:

> "Pivotal CRC [colorectal cancer] program issues—Single agent activity. The trial which is ongoing will need to be shared with us. We should attend the FDA meeting with ICE [ImClone] when the data is final. There is no agreement that we could find that is reassuring regarding activity level needed for approval.
>
> "Weak dose selection rationale—They have developed a PK [pharmacokinetic] rationale for dose selection, however the dose is questionable for refractory patients and the safety margin for early stage patients has not been determined. In their phase 3 first line study they are evaluating the same dose used in refractory disease. This is already seen as a problem by the FDA and by us . . .
>
> "Safety—The safety of the product, specifically related to skin toxicity, bleeding, allergy has not been well characterized. This reemphasizes the weakness of the dose selection argument . . ."

Ultimately, concerns about the single-agent study and the 9923 study were not completely resolved before BMS entered into the agreement with ImClone. In a

June 12, 2001 "Summary of Key Findings," BMS executives pointed out the risks of the results of the single-agent study:

> "FDA has requested that data be provided on the antitumor activity of C225 as a single agent. Preclinical data has thus far been provided to FDA to address this issue, but they have persisted in their interest that clinical data be provided. *No accelerated approval has ever been granted for an oncology drug for use in a combination therapy.* (emphasis added). In the event that tumor responses are observed in the ongoing single-arm single agent refractory colorectal study then it is possible that this could throw into question the approvability of the combination claim based on nonrandomized antitumor data (given that the value of CPT-11 after CPT-11 might be questioned)."

On September 4, 2001, a BMS Vice President sent an e-mail to other senior BMS executives, stating:

> "Based on today's discussions with Susan and Steve our preliminary recommendation is a 'go' decision. We are still trying to obtain data from the mono therapy study from ICE [ImClone]. As of 6:30 PM today we did not have any more information. I will be discussing this with Susan again in the AM."

Despite requests to BMS, Committee staff has not been provided any evidence at this time that shows that BMS obtained the data on the single-agent study prior to making its historic deal with ImClone.

In addition, the BMS independent radiology review of ImClone 9923 study lowered the ImClone reported response rate and the size of the patient pool, both significantly. In an August 30, 2001 e-mail, the BMS independent radiologist noted:

> "Attached to this message you will find the latest update of the spread sheet we are using to keep track of our review of the CT's and MRI's of patients enrolled in CP02-9923.
>
> "We are in the process of reviewing a total of 34 cases, 27 of which were initially assigned by the investigator to the PD [progressive disease] cohort and 7 of which were assigned to the SD [stable disease] cohort. To date we have reviewed 23/27 cases from the PD cohort and 6/7 cases from the SD cohort.
>
> "In the PD cohort we can now confirm 14 partial responses. We may have 15, but one case will require adjudication. With 4 more cases to review, and the one case for adjudication, the RR in the PD cohort could be as high as 15 + 4/120 = 15.8%.
>
> "I should mention, however, that in 4 of these confirmed partial responses our radiologists have judged the disease to be only stable at the time of patient's enrollment into the study. If these 4 cases were thrown out, then the highest possible response rate would 11 + 4/120 = 12.5%. However, we have not conducted a strict review of all of the 120 cases, and *it is likely that if we carefully reviewed all of the cases we would throw many out on the same basis* [emphasis added]. Indeed, it is my understanding that the study sponsor has conducted such an analysis on the basis of its own radiologists' review, and has thereby reduced the denominator of the patient population with radiographically confirmed progressive disease.
>
> "I will review the study sponsor's data and see if I can get at the same denominator [patient pool size] as it did (? N = 89), and calculate the response rate accordingly. More cases and analysis to follow tomorrow... "

It should be noted that, if indeed the denominator in 9923 was below 100 (particularly if it were as low as 89, which the BMS independent radiologist appears to have indicated in the above e-mail), the entire study probably could no longer serve to support an accelerated approval application. As ImClone consultant, Roger Cohen MD, e-mailed to Dr. Harlan Waksal on January 4, 2002:

> "9923 is a small study to begin with. It cannot get much smaller and have any hope of serving as a registration study. I think it is clear that it has to have at least 100 fully eligible and evaluable subjects (closer to 100)."

Therefore, although BMS received tentative support from its scientific leadership and outside consultants, it appears that the status of crucial issues were as follows at the time BMS entered into the alliance with ImClone in September 2001:

1. Single agent activity—BMS lacked the data from the single agent study.
2. Response rate—BMS outside radiology review indicated that a strict review could lower the response rate below the clinically meaningful standard of 15 percent.
3. The denominator, or patient pool size, of the pivotal trial appeared to be under 100, and therefore could not serve as a basis for accelerated approval according to ImClone's own consultant.

BMS REACTION TO IMCLONE COMMENTS ON THE REFUSAL-TO-FILE LETTER

On the evening of December 28, 2001, ImClone revealed to the public that it had received a refusal-to-file letter from FDA. On December 29, 2001, a Reuters news article reported: "Sam Waksal, ImClone's chief executive officer, told Reuters that the agency first wants more 'annotation' information, about how the company verified that patients enrolled in its trials had indeed failed previous drug regimens and that subsequent tumor reductions attributed to Erbitux were indeed real. Concerns raised by the FDA mainly involve how the data were presented and do not raise outright concerns about safety or efficacy of the drug, the CEO added." An internal BMS e-mail dated December 30, 2001, responding to earlier BMS e-mails on the Reuters article, states: "I agree that some alot [sic] of Sam's comments are misleading and at this point we should continue to be silent. As you heard from yesterday's discussion, there's a lot we don't know."

On that same date, December 30, 2001, another BMS official commented on the draft documents being prepared for the ImClone investor relations conference call: "These draft documents leave me most uncomfortable. They gloss over the seriousness of the RTF letter and make it appear that the integrity of the study results is not in question, when in fact it is . . . We will also need to rewrite major portions of the clinical and pharmacology part of the BLA including a new 9923 study report, new 141 (monotherapy) study report, new ISS and ISE based on these revised reports. I know that this is not what ImClone wants to tell their investors, but I think it represents the reality of this situation."

TRADING ACTIVITY OF SAM AND HARLAN WAKSAL, THEIR FAMILY MEMBERS AND CLOSE FRIENDS, AND IMCLONE DIRECTORS

Adding to the controversy over Erbitux has been the trading of ImClone stock by ImClone insiders a few weeks before the FDA refusal-to-file letter, and by Waksal family relatives and friends during the 48 hours before the FDA letter was issued. Committee staff examined public records and conducted interviews with Sam and Harlan Waksal, and with representatives of several of their family members and friends, to determine the degree of trading in ImClone stock by these individuals over the last year. Of particular interest were board members who tendered stock to BMS on October 29, 2001, and whether any board members or officers of ImClone sold stock during the critical month of December 2001. Committee staff also attempted to gather information on those trades of Sam Waksal's immediate family members and close friends that were identified during discussions with Dr. Waksal.

Committee staff found that ImClone board members exercised stock options to acquire 8.1 million shares of ImClone common stock between the period of June 1, 2001 and October 29, 2001. Committee staff examined this time period because it represents the period of negotiations between BMS and ImClone officials regarding an equity purchase of ImClone by BMS. Of these 8.1 million ImClone shares, Sam and Harlan Waksal acquired approximately 4.1 million. Each board member who exercised stock options during this time period is shown in the table below.

ImClone Incorporated Stock Options Exercised by ImClone Board Members During the Period of Negotiations with BMS

June 1 Through October 29, 2001

ImClone Board Members	Date Exercised	Shares	Options excercised at
Barth, Richard	6/13/2001	2,500	$3.00
Barth, Richard	9/17/2001	2,500	$3.00
Barth, Richard	10/29/2001	27,328	$4.50
Devita, Vincent	N/A		
Goldhammer, Robert	7/16/2001	316,684	$.28-$6.63
Kies, David	8/2/2001	30,000	$6.63
Kies, David	7/25/2001	55,000	$3.00-$5.44
Kopperl, Paul	7/24/2001	120,000	$3.00-$6.63
Kopperl, Paul	10/29/2001	6,430	$39.91
Levine, Arnold	8/3/2001	16,000	$5.43
Mendelsohn, John	10/29/2001	90,226	$.53-$2.75
Miller, William	N/A		
Waksal, Harlan	7/12/2001	2,080,000	$3.03-$9.13
Waksal, Sam	7/12/2001	2,060,000	$5.69-$9.13
		4,806,668	

It should be noted that ImClone awarded many of these options to the Waksal brothers in 1999 and 2000, and accelerated the vesting of these options with the rise in the stock price. According to ImClone's SEC filings, on May 24, 1999, the stockholders approved the grant of an option to Sam Waksal to purchase 1,000,000 shares and Harlan Waksal to purchase 650,00 shares of Common Stock at a per share exercise price equal to $18.25, the last reported sale price of the Common Stock on the date shareholder—approval was obtained at the annual shareholders meeting. The option was to vest no later than six years from the grant date and specified amounts were subject to earlier vesting if specified Company Common Stock price thresholds were met. On May 31, 2000, the stockholders approved amendments to a total of 1,600,000 options that were granted to Sam and Harlan Waksal the year before. The shareholders also approved amendments to a total of 3,300,000 additional options held by Sam and Harlan Waksal. All these options were amended to provide that each tranche vested immediately upon achievement of the relevant stock target price associated with such tranche, without regard to the passage of time that was a requirement in the original options. The options became fully vested and exercisable upon the approval of the amendments. As reported in a previous section, the ImClone board granted the Waksal brothers and two other directors company loans to finance the exercise of their options as part of the tender offer.

In total, Committee staff found that members of ImClone's Board of Directors tendered 2.1 million shares of ImClone common stock at $70 a share to BMS on October 29, 2001. This represents approximately 15% of the stock tendered by ImClone shareholders to BMS. Sam and Harlan Waksal tendered a total of 1.6 million shares of ImClone stock to BMS for about $111 million. Simply stated, this means that the Waksal brothers received over 10 percent of the entire proceeds paid by BMS during the $1 billion tender offer, and the ImClone Board combined received nearly 15 percent of the proceeds from the BMS tender offer. The table below shows the number of shares tendered and the proceeds for each of ImClone's Board members.

ImClone Incorporated Shares Tendered to BMS by ImClone Board Members

October 29, 2001

ImClone Board Members	Shares Tendered	Cost Per Share	Proceeds
Barth, Richard	27,328	$70	$1,912,960
Devita, Vincent	129	$70	$9,030
Goldhammer, Robert	364,781	$70	$25,534,670
Kies, David	30,007	$70	$2,100,490
Kopperl, Paul	27,864	$70	$1,950,480
Levine. Arnold	1,329	$70	$93,030
Mendelsohn, John	90,226	$70	$6,315,820
Miller, William	8,573	$70	$600,110
Waksal, Harlan	776,450	$70	$54,351,500
Waksal, Sam	814,674	$70	$57,027,180
	2,141,361	$70	$149,895,270

Committee staff also examined trading by ImClone board members and officers during the critical month of December 2001 to determine if any ImClone officials who sold stock had knowledge of discussions with FDA regarding whether the agency would accept the Erbitux filing. We found that, with the exception of Harlan Waksal's disposition of 700,000 shares on December 6, 2001 (discussed below), three officers of ImClone sold stock prior to December 18, 2001. In each case, Committee staff were told that the officials involved were unaware of the details of the FDA review of Erbitux, sold less than 20 percent of their holdings in ImClone, and did so based on their brokers' advice. Even though ImClone has internal rules that require officers of the company to receive pre-clearance before trading in company stock, two of the three trades were not pre-cleared. In one case, the individual was not an officer at the time of the trade, but was since promoted. In the other case, the officer claimed to have simply forgot to pre-clear the trade.

On December 21, 2001, ImClone issued an order prohibiting its employees from trading in ImClone stock until after the FDA decision on Erbitux was made public. ImClone has told Committee staff that no board member or officer of ImClone traded ImClone stock between December 21 and 28, 2001. However, Committee staff discovered that several of Sam Waksal's immediate family members or friends sold ImClone stock on December 27, 2001—the day before ImClone announced publicly that FDA had refused to accept the filing of Erbitux. This list of traders included

his father, sister, two daughters, and son-in-law. In addition, Committee staff learned from discussions with Sam Waksal that the SEC has questioned him about trades made by three other friends on December 27 or 28, 2001.

With the exception of Sam Waksal's father (who has not yet provided information to the Committee), attorneys for each of the family members admitted that their client sold stock on or around December 27, 2001, but asserted that they received no non-public information about ImClone and each had a reason why they sold the stock on that particular day. Although phone records and logs obtained from Sam and Harlan Waksal, covering the time period December 26-28, 2001, suggest that both men had conversations with each other and may have had conversations with members of their family and friends, both Sam and Harlan Waksal denied that they had tipped off anyone as to their knowledge that ImClone was about to receive a RTF letter from FDA.

On December 6, 2001, Harlan Waksal sold 700,000 shares of ImClone stock. On October 31, 2001, Harlan Waksal notified the ImClone board members that he planned to execute a forward transaction involving 700,000 shares of ImClone common stock:

Dear Members of the Board:

As a result of my recent option exercise and the sale of stock to Bristol-Myers Squibb I am left with an additional tax burden that I need to meet. As I am averse to having such a great personal liability I plan to meet this obligation (and provide some liquidity), by the sale of additional shares of ImClone stock. I am moving to do this through a prepaid forward contract for the sale of stock. This will be a 700,000 share transaction, the stock will still be under my voting control for the next three years and I will retain some continued upside if the stock continues to perform as we anticipate. I plan on finalizing this transaction over the next two weeks.

I look forward to seeing you at the Board dinner on the 14th.

Sincerely,

Harlan W. Waksal, M.D.

Dr. Harlan Waksal told Committee staff that, in November 2001, he attempted to shop the sale of his ImClone stock. Dr. Waksal filed a Form 144 with the SEC, announcing his intention to sell 700,000 shares of ImClone. Dr. Waksal told Committee staff he was forced to sell the ImClone stock to come up with enough cash to pay substantial taxes generated from his prior exercise of stock options and his tendering of shares to BMS. He also stated that, because he did not want to sell shares, he entered into a forward sales contract that gave him a percentage of the cash value of the shares up front but still allowed him to control the shares and defer tax payments for another two years. Simply put, Dr. Waksal received less than what the stock was worth at the time of the sale, but he also limited his downside risk when ImClone's stock price dropped considerably in the month thereafter. It should be noted that Dr. Waksal sold the 700,000 shares on the same day that ImClone's share price hit its 52-week high.

Moreover, in February 2002, Dr. Sam Waksal revealed about 50 unreported stock trades that should have been reported to the SEC and returned to ImClone about $486,000 in profit he made on some sales of company stock because he may have violated an insider-trading regulation.

CONCLUSION

The key findings from the Committee staff's investigation at this point are as follows:

- In August 2000, the primary FDA medical reviewer handling the ImClone/Erbitux matter did not believe that ImClone's 9923 study met the criteria for accelerated approval and fast-track designation. Her view is substantiated by the opinions of leading oncology experts who reviewed the 9923 protocol for the *Cancer Letter* in 2002 and found serious protocol design flaws.
- At the August 11, 2000 meeting between ImClone and FDA to discuss a possible accelerated approval strategy, FDA relied on the wrong version of the 9923 protocol, which had a tighter inclusion criteria than the one actually used in the amended protocol. ImClone did not correct FDA's mistake.
- At the same August 11, 2000 meeting, the senior FDA medical official in effect overruled the primary medical reviewer and said the protocol design was probably acceptable.
- The senior FDA official now believes she was misled by ImClone about its claim that a human clinical trial showed no single agent activity. This official said that this claim was a key factor in her decision to allow ImClone's application to proceed.

- FDA's decision to grant fast-track designation to ImClone's Erbitux appears to have been based on the wrong version of the 9923 protocol, and was made before it had the single-agent data on Erbitux.
- The 9923 study was afflicted with many problems. The BMS independent radiology review showed that strict scrutiny of the study data resulted in a response rate of only 12.5% (as opposed to the claimed 22.5% response rate) and that the number of evaluable patients was only approximately 89 (as opposed to the original 120). If these data were in fact correct, the 9923 study failed to meet the 15 percent clinical endpoint set by ImClone and the study would be too small to support an accelerated approval by itself.
- BMS scientists were aware of the issues involving the response rate and the size of the patient pool, and BMS apparently did not have the single-agent data prior to entering into its agreement with ImClone in September 2001. Nevertheless, BMS went ahead with the ImClone agreement.
- The results of the single-agent study showed enough activity in Erbitux alone to throw into doubt the assumption used for the pivotal 9923 study—that the toxic chemotherapy, irinotecan, needed to be used in combination with Erbitux to produce stronger and more meaningful response rates. Because of this doubt, FDA needed additional studies to resolve this issue, which would mean a substantial delay in launching Erbitux.
- ImClone knew the results of the single-agent study on October 12, 2001, but its then-CEO appeared to portray these results in a positive light to the BMS Chief Scientific Officer.
- On October 29, 2001, BMS consummated the tender offer with ImClone. As a result, Sam and Harlan Waksal made about $111 million from the sale of stock. In acquiring their shares, the Waksal brothers had received loans from ImClone to finance the exercising of options.
- On November 30, 2001, key FDA reviewers recommended a refusal-to-file letter for the Erbitux application.
- On December 4, 2001, ImClone's Regulatory Affairs Vice President confirmed in a conversation with one of the FDA reviewers that an RTF letter is a realistic possibility.
- On December 5, 2001, senior FDA management at the Center for Biologics determined that an RTF letter would be sent to ImClone. It took several days for all members of the FDA review team to learn of this decision and it did not become official until a team meeting held on December 17, 2001.
- On December 20, 2001, FDA informed ImClone and BMS that a decision had been reached and that the decision letter would be sent on December 28, 2001. ImClone and BMS officials suspect an RTF.
- On December 24, 2001, an outside consultant to BMS obtained confirmation from an FDA official that an RTF letter will be issued.
- On December 25, 2001, a BMS executive informed Dr. Harlan Waksal that ImClone would be getting an RTF letter.
- On December 26, 2001, key ImClone and BMS officials were aware of the RTF. ImClone sent a letter to FDA to try to prevent the RTF letter.
- On December 27 and 28, 2001, Waksal family relatives and some friends sold ImClone shares.
- On December 28, 2001, ImClone received the RTF letter.

Report to House Committee on Energy and Commerce

by

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My Background

Since finishing all postgraduate training in internal medicine and the subspecialty of medical oncology, I have spent the past 30 years in clinical academic practice. I have been on the faculty of three medical schools, one of which was full time (in the 1970s) and the other two, part time. I also spent 3.5 years in a senior administrative position at the National Cancer Institute (NCI) and 15 years as the civilian Chief of Medical Oncology at the Walter Reed Army Medical Center (WRAMC). Since 1996 I have been an independent consultant in oncology for a variety of contracts with Federal Government agencies and several private organizations. Since 1981 I have been the Chair of the Data Audit Committee of the Cancer and Leukemia Group B (CALGB), one of the collaborative research organizations funded by the NCI for testing new treatments for a variety of cancers. In the past six years since leaving full-time employment with the Federal Government I have continued this work under a contract with the University of Chicago that is supported by a grant from the NCI. This role involves directing and managing the 20 members of this committee, which makes site visits at least once every 36 months to the nearly 300 institutions participating in CALGB research around the country, auditing the medical records of patients entered on the research protocols. The CALGB accrues 4500+ patients a year to 70+ research protocols ongoing at any one time covering a broad selection of cancers. In addition, I also do this sort of quality assurance work under an NCI contract with the Cancer Trials Support Unit, another entity funded by the NCI to conduct clinical trials with new treatments for cancer. Over the past 21 years in this role as an auditor of scientific research I have personally reviewed the medical records of several thousand patients. I have also been a consultant to review and analyze five instances of fraudulent clinical research involving patients with cancer. Finally, since graduation from medical school I have 37 years of experience caring for patients with all forms of cancer, and I presently work part-time in this capacity at the Walter Reed Army Medical Center and at a private practice with offices in both Westminister, MD and Gettysburg, PA. In the latter venue I personally care for patients with various stages of colon cancer, including widely metastatic disease. For these patients I personally use chemotherapy (including irinotecan) in the hope of palliating their disease and adding some extra months to their survival.

Disclaimer

I neither own any stock in ImClone nor know the principals personally. I do not own any stock in Bristol-Myers Squibb (BMS). I am acquainted with several BMS officials involved in development of new oncology drugs. A living trust in my wife's name holds 15 shares of BMS stock (present value about $425), but this account is professionally managed, and she has absolutely no input to any of the financial transactions or decisions to buy or sell shares held in any company in this trust portfolio. In 1993 to 1994 I was the Principal Investigator for a Phase I clinical trial with a new BMS compound while I was employed full time at WRAMC. BMS provided $30,000 to the WRAMC Department of Clinical Investigation for support of this research (and not to me personally). I was supported by BMS to speak at the 13th Bristol-Myers Squibb Nagoya International Cancer Treatment Symposium sponsored by BMS and held in Nagoya, Japan in October 1997. Other than these items I have had no interaction with BMS. I do know and hold in high esteem some of the oncologists who have been participants in the clinical trials sponsored by ImClone.

Statement of Work

The House Committee initiated a review of the clinical trial undertaken by ImClone Systems, Inc. to assess the efficacy and toxicity of a new agent known as cetuximab (Erbitux®, C225) developed by this company for the treatment of metastatic colon cancer. The Committee engaged my services as a physician consultant with experience reviewing clinical research involving new agents for cancer treatment. This Committee investigation grew out of the fact a Refusal to File (RTF) Letter was sent to ImClone by the FDA on 28 December 2001 denying further review of their Biologic Licensing Application (BLA) for accelerated approval of cetuximab. A concern was raised that inappropriate financial transactions by company officials may have taken place in the latter part of 2001, especially around the time of the RTF action. A part of this matter involves the possibility of hyperbole in discussions of this new agent by ImClone officials, especially in regard to its efficacy for colon cancer and how speedily marketing approval would be granted by the FDA.

In my capacity as consultant to the Committee staff I was provided access to a number of the items acquired by the Committee, including case report forms of some of the patients who were said to have responded to cetuximab, confidential communications by ImClone and Bristol-Myers Squibb (BMS) officials, confidential communications by FDA officials, and radiographs of some patients. All items involving patients had names and other identifiers redacted. My charge by the Committee staff was to assess certain aspects of the clinical trial entitled 9923. A copy of the protocol for 9923 was provided as part of my review. One version was 1.0 and was dated 2 August 1999. The other version was 2.0, dated 18 October 1999. In addition, I acquired a number of items myself including media discussions of cetuximab and articles published in the medical literature regarding colon cancer treatment and the preclinical development of cetuximab. My work involved multiple visits to the Committee offices and lengthy discussions with Mr. Alan Slobodin, the lead Committee staff member assigned to this investigation. I reviewed the radiographs of three patients entered on 9923 with a radiologist at WRAMC who is experienced in the interpretation of CT scans of the chest and abdomen.

The Clinical Problem

Colon and rectal cancers are the second (after lung cancer) most common cancer in the U.S. when both sexes are combined. Some 60,000 people will die of this disease in the U.S. this year. Approximately half of all people who develop this cancer will have metastases (spread) of the cancer distant to the primary cancer site in the large bowel or rectum. The liver is the most common site for this cancer to spread. Only a small fraction of patients (perhaps 5%) will not succumb to this cancer once it has spread to other organs. The median survival after the appearance of metastases is approximately nine months with only a rare patient surviving more than three or four years later. The only patients who are cured of metastatic colorectal cancer (CRC) are a very fortunate subset (only some 15% of all patients with metastases) who have isolated metastases in the liver feasible to remove surgically and who survive without developing further metastases (only a third of those undergoing such resection surgery).

Since 1959 and until 1996 only one drug had established efficacy for treatment of metastatic CRC, 5-fluorouracil (5-FU). Therapy with this agent has been demonstrated to improve both the overall and symptom-free survival of patients with metastatic CRC when compared to supportive care alone without active antitumor treatment.[1,2] In the 1980s a drug that modulates the metabolism of 5-FU (leucovorin) was found to increase the percentage of patients who achieve significant remissions of their metastatic cancer, but it has not further improved the overall survival of such patients treated with 5-FU. In 1996 another agent, irinotecan (Camptosar®, CPT-11), which was originally developed in Japan, was approved by the FDA for treatment of metastatic CRC. Now two drugs were available to treat patients with metastatic CRC. Not only were there published studies that established the efficacy of 5-FU/leucovorin as initial therapy, but now there were trials[3-6] that established irinotecan as an effective second-line therapy, once a patient's cancer was proven to be unresponsive to further 5-FU/leucovorin therapy. However, unfortunately once both these drugs are no longer effective, there is no other systemic therapy available to treat patients with this ultimately fatal cancer.

Cetuximab Preclinical Development

Cetuximab is an antibody designed to bind with, and block, the Epidermal Growth Factor Receptor (EFGR), which lies on the surface of cell membranes. The action of the antibody is to block this receptor and therefore ultimately interfere with cell division and proliferation. There is a strong scientific basis for designing drugs to interfere with the action of this receptor.[7] It is known that these receptors are frequently overexpressed by cancer cells, and it is known that when such overexpression occurs, the cancer tends to proliferate and spread faster. Already one such antibody, known as trastuzumab (Herceptin®), has been established as being a useful drug for the treatment of breast cancer and is marketed for that indication. This agent also has promise for efficacy in a variety of other cancers and is in clinical trial for such evaluation. With receptor-binding antibodies having a strong theoretical basis for anticancer therapy and one instance of high efficacy in the clinical setting, a number of biotechnology companies have developed other antibodies to elements of the family of EGFRs.[7] Some are probably close to FDA approval for marketing, while others are still in clinical trials.

Approximately 20 years ago Dr. John Mendelsohn created a panel of mouse antibodies to EGFR while he was a faculty member and cancer center director at the University of California at San Diego. He continued his work with this set of antibodies while chief of the Department of Medicine at the Memorial Sloan-Kettering Cancer Center in the 1990s and more recently as CEO of the M.D. Anderson Cancer Center in Houston. The original mouse-derived antibody is immunogenic and likely to induce antibodies against it when administered to human beings that would either cause serious allergic reactions and/or inactivate the antibody so no antitumor effect can occur. Thus, cetuximab was developed as a human:murine chimeric[8] (meaning two originating elements) of the mouse (murine) antibody that Dr. Mendelsohn created.

All new agents that might have benefit for treatment of human cancers must traverse an extensive process of evaluation in the laboratory setting. Such laboratory work with cetuximab suggested efficacy against colon cancer, and when used in combination with irinotecan, even greater antitumor effect was demonstrated.[9] It also had antitumor effect against renal (kidney) cancers and cancers of the head and neck area in such laboratory testing. This agent had significant promise for being an effective drug in treatment of human cancers, especially CRC.

The 9923 Protocol

This study was an open-label, phase II study designed to "determine the response rate of cetuximab administered in combination with irinotecan to patients with advanced colorectal cancer who are refractory, i.e., have demonstrated stable or progressive disease to treatment with an irinotecan-containing regimen" and "to determine the time to progression, evaluate the safety/toxicity profile of cetuximab in combination with irinotecan [and] assess the Quality of Life" in patients treated with this two-drug combination. "Refractory" to prior therapy means that an adequate attempt to cause tumor regression with a particular therapy has been made, and the cancer progressed despite the treatment. Version 1.0 of the protocol was dated 2 August 1999. Version 2.0 was dated 18 October 1999. It was not originally designed to be a study used as the basis for submission of a BLA for marketing approval. After accrual of most of the patients entered and discussions with the FDA by ImClone officials in 2000, the purpose of the clinical trial was modified so it would serve as a registration study. A meeting was held between ImClone and FDA officials in August 2000 at which time the understanding was that 9923 would be the registration study with a plan for accelerated approval designation. A study used for submission to the FDA for marketing approval (i.e., "a registration study") would have adequate numbers of patients entered to provide proof of the efficacy and safety of the new drug, and the study would be very tightly controlled and conducted so that errors in its conduct or uncertainties about the results would not be issues.

The patient eligibility criteria for any clinical trial are extremely important. Without carefully defining what category of patient is eligible for entry on such a study, any results from the trial will be subject to various biases and likely be meaningless. In addition, the exact method of administering the drugs (dose and schedule) must be defined and adhered to. The eligibility criteria in Version 1.0 stated the patient must have demonstrated "progression of disease [metastases] after

completing a minimum of two courses of a regimen containing irinotecan." The definition of a "course" of irinotecan was not stated. These eligibility criteria were changed in Version 2.0 of the protocol. In the newer version the patient had to have "documented stable disease (must have received a minimum of 12 weeks of irinotecan therapy) or progressive disease at any time after receiving an irinotecan-containing regimen." The irinotecan dose and administration frequency were to be the same as was being used for the patient when progressive disease occurred prior to entry on the trial.

Documents regarding the August 2000 FDA meeting indicate FDA officials had concerns about the study design and whether there was sufficient documentation a patient had clearly failed irinotecan therapy before study entry. The whole scientific basis for clinical use of this new drug was that the combination of irinotecan and cetuximab represented a potentially effective, third-line therapy for patients with metastatic CRC after failing prior 5-FU and irinotecan therapy. The ImClone officials stated their belief that "there exists a core of patients who had clearly refractory disease for whom the evidence of antitumor activity is compelling" in the results of the study conducted to that time point. In order to prove that both drugs had to be administered together to obtain an antitumor effect (while accepting the potential for toxicity of both drugs), the patient's cancer had to demonstrate clear resistance to any further therapy with irinotecan. The eligibility criteria as understood by FDA officials (according to minutes of the meeting in August 2000) were that patients would have to have either stable disease defined as <25% volume change in the measurable cancer lesions or progressive disease defined as a >25% change "after two courses of irinotecan." This latter point is what the protocol Version 1.0 stated. There is a difference in the definition of what constitutes an eligible patient between Version 2.0 of the protocol and the understanding of the FDA officials at this meeting. Version 2.0 (dated 18 October 1999) loosened the eligibility requirements to "progressive disease at any time after receiving an irinotecan-containing regimen." No minimum amount or duration of therapy with irinotecan was required in Version 2.0. The final conclusion of the FDA officials was that the study design was "probably acceptable."

Study 9923 Conduct

There were 139 patients entered on 9923, 121 with progressive cancer after irinotecan and 18 with stable disease. Somewhere one patient was deleted, because all reports subsequent to 2000 indicate there were 120 patients with progressive disease who were treated on this study.

During the study a contract research organization (PharmaNet) had research monitors verifying the data collected at the participating institutions. There were a number of deviations from the study protocol cited by these monitors, but in my opinion many were trivial in nature (e.g., being one day off in recording the date of a blood test). However, there were some that appear to be substantive, such as entering patients who did not meet the eligibility criteria. In January 2002 BMS staff reviewed and critiqued the BLA. According to Table 1 of this review an incredible 37 patients (26.6% of the 139 patients entered) "had at least one inclusion/exclusion" criterion "that did not qualify them to be eligible for the study," and eight of them "had more than one reason for ineligibility." Twenty-five of these 37 patients had initial blood counts or serum chemistry values that were outside the range required by the protocol. Another incredible point is the fact that 15 of these 25 patients "were given exemptions to be enrolled in the study." The purpose of eligibility criteria for a study is to define what patients have organ function and disease parameters that make them a suitable candidate for the clinical trial. Once these criteria are set, exemptions are <u>not</u> given to allow patients to be entered who don't meet the established criteria. If this is done, it could invalidate the results of the study. If the criteria are too restrictive, thus making it difficult to enroll patients who meet them, one might amend the study to loosen the criteria or perhaps just stop the study as being unworkable. Eligibility exemptions are forbidden in all the clinical trials with which I have experience. Rates of ineligibility should not be more than single digit percentages in any clinical trial. When an ineligible patient is entered, it is usually an error on somebody's part in which a particular point was overlooked or forgotten and should be an uncommon event.

Another set of major deviations in the study was changing the dose and administration frequency of the irinotecan. This drug was supposed to be administered in the same pattern as had

been done before the patient went on the 9923 study. Irinotecan is most often administered in a schedule of four consecutive weekly doses, with a 14- to 21-day break before another series of four consecutive weekly doses is begun. However, it may also be given in a schedule of once every three weeks. Thus, there were variations in the manner patients might receive the irinotecan on the study. There are directions in the 9923 protocol regarding delaying one or more of the weekly cetuximab infusions for any significant toxicity that might occur, but there were no directions for modifying the irinotecan dose or frequency. The treating physician would thus make ad hoc decisions regarding this point, with multiple variations based on the physician's best judgement. It is standard practice in cancer treatment protocols to provide specific directions for changes in the drug doses and/or treatment frequency based on the degrees and kinds of therapy toxicity encountered. In my opinion this point is a design flaw in the 9923 protocol that could lead to problems in interpreting the results.

The protocol deviations in the irinotecan dosing were delineated in Table 3 of the BLA review by BMS staff. Although the protocol specified that the irinotecan was to be given in the same dose and schedule as previously when disease progression occurred, with no dose increases, at least 17 patients had major changes in the irinotecan dose when entered on the study, including dose increases. This fact adds further uncertainty regarding the validity of any results from this study.

Flaws in the design of the 9923 protocol were also expressed publicly by three prominent medical oncologists after the publication of the RTF.[10] For example, one oncologist stated: "Overall, this is a protocol that asks the wrong questions, and then is not tightly written and efficient. The protocol generates far more questions than it could ever answer. It is a blueprint for the production of vague answers."[10] Another oncologist stated that "the entry criteria on the study were so vague it can't be determined whether all the patients in the trial are indeed refractory to prior therapy."[10]

Results of 9923 Study

An independent panel of two medical oncologists and two radiologists was convened by ImClone to review the case records and the radiographs (the Independent Response Assessment Committee or IRAC) and evaluate the responses, or lack thereof, of all patients entered whether counted as "progressive disease" or "stable disease" on the irinotecan therapy given prior to study entry. Many of these same radiographs were then reviewed by consultants to BMS. A comparison of these two sets of evaluations indicates the subjectivity that can occur in making assessments of the same CT scans. As with much of medicine, assessing response of cancer lesions to therapy is not an exact science. For example, eight patient cases the IRAC had categorized as achieving a Partial Response (PR), which is defined as at least 50% regression of the measurable tumor lesions visible on serial radiographic studies (almost always CT scans), were categorized by the BMS consultants as achieving only stable disease (SD). A total of 23 patients were categorized as achieving a PR by the investigators, while 27 were so categorized by the IRAC. Twenty of these patients were considered to have a PR by both the investigators caring for the patients and the IRAC for an overall response rate of 16.5%. Of the 121 patients coded as having disease progression prior to entry, the IRAC and BMS agreed that a PR had been achieved in only 16 cases. Now the response rate was only 13.2% where both sets of consultants agreed. In addition, three patients whose response after treatment with irinotecan and cetuximab was called SD by the IRAC had it changed to "progressive disease" by the BMS review. The number of responders where both BMS and the IRAC would agree with the interpretation of the scans is now possibly below the point of real meaning. Most clinical oncologists would agree that at least 15% of patients treated with an agent should achieve a PR to be meaningful. In fact, the ImClone officials themselves discussed with the FDA officials in the August 2000 meeting that at least a 15% response rate must be achieved to be "clinically meaningful." A response rate lower than 15% would only be important if a randomized study with half the patients receiving a new treatment and half receiving only supportive care indicated a significantly longer survival for the treated group. Such is indeed the case with irinotecan, as has been established scientifically.[3,5,6] Although the response rate of irinotecan in patients who had failed 5-FU therapy was only approximately 13%,[3] overall survival was significantly improved by irinotecan therapy when compared in a randomized study to supportive care only (without systemic anticancer therapy).[5,6] Of course, such could also be the case with cetuximab if it were subjected to the same sort of randomized study as has been accomplished with irinotecan.[5,6]

In the context of the disparities regarding which patients achieved a response and to what degree, it is worth quoting the statements made by Dr. Sam Waksal at a conference call to the financial community on 31 December 2001. He said the IRAC came to a similar conclusion about responders as did the investigators. He further stated that all CT scan films had been reviewed "internally by us, they have been reviewed by the sites themselves where the conclusions were made and by the IRAC, and again there is *concordance across the board*"(italics are mine). Overall, there were 38 patients where the category of disease status prior to study entry was in disagreement between the IRAC and the investigators. In addition, of the 35 patients whose radiographs were reviewed by BMS consultants, there was disagreement between the IRAC and BMS consultants in the response category for 14 cases, which is more than a third of the sample.

The results of this study were published in an abstract[11] submitted for the annual meeting of the American Society of Clinical Oncology, held each May. This society is the premier organization worldwide for professionals involved in cancer research and the treatment of cancer in patients. The abstract submission deadline is early in the month of December prior to the meeting (in this case it would have been December 2000). The abstract stated that the patients were refractory to both irinotecan and 5-FU, and 121 patients were said to have been entered.[11] Whenever any study data are presented at this meeting, only 10 minutes are allowed for the oral presentation. Thus, only a limited amount of information can be presented. It was stated patients were entered who had "documented progression of metastatic disease on irinotecan" and " no intercurrent chemotherapy could have been given between irinotecan failure and protocol entry." The abstract states 121 patients were entered, but the oral presentation involved only 120 patients. A total of 27 of these 120 patients (22.5%) were said to have achieved a PR, which is the number determined by the IRAC.

Case Reviews

I reviewed with the WRAMC radiologist the film sets of the three cases where selected CT scan pictures of metastatic lesions were shown at the ASCO presentation. These were Cases #615, #644, and #683. It is noteworthy that Case #644 was coded as having achieved only a SD status by the IRAC after treatment on the study. Although this patient indeed had regression of some metastatic lesions in the lungs, a pelvic mass was at the same time invading and encroaching more on the urinary bladder in the pelvis. It is also noteworthy that Case #615 had irinotecan therapy only from 15 November 1999 to 6 December 1999, and assuming the drug was given weekly, only four doses could have been given. A chest X-ray done on 4 January 2000, a month after the last irinotecan dose, did indeed show a new nodular density in the right mid lung, indicating cancer progression. Although this patient did meet the revised eligibility criteria of the study in Version 2.0 of the protocol, he would not have been eligible based on the understanding of the FDA of the eligibility criteria where the patient would have had to be treated with "two courses" of irinotecan. If the drug is given weekly in four consecutive weeks, then this would constitute a "course." A second "course" of four weekly doses would then be given after a rest interval without treatment of 14 to 21 days. This patient did not receive two courses of irinotecan therapy prior to entry on the 9923 study.

An example of clear ineligibility for this study is Case #643. This patient received his last dose of irinotecan on 31 March 1999. He was then treated with oxaliplatin (another investigational agent for CRC) between June 1999 and August 1999. It must be recalled that according to the protocol no other chemotherapy should have been administered between the time the patient was last treated with irinotecan and the time of study entry, a point that was reiterated in the ASCO abstract presentation.[11] Nonetheless, he was entered on the study on 14 March 2000.

Another example of problems with this study is Case #704. The ASCO abstract[11] states the patients were refractory to both irinotecan and 5-FU. The case report form for this particular patient indicates that the only chemotherapy the patient had received prior to study entry was irinotecan. There is no evidence the patient ever received 5-FU.

The serial radiographs of Patient #683 were reviewed. This patient had clear progression of his cancer on irinotecan, so he met the eligibility criteria of 9923 in this regard. In response to the 9923 therapy he had definite shrinkage of the cancer lesions in the liver, which regressed at least

50%, but the response lasted only three months before disease progression occurred once more. This is a rather short interval, but one must recall the patients treated on this study had undergone much prior systemic therapy and sometimes radiation therapy also. Such a short interval of response would be expected from a drug with some modest antitumor efficacy but not one that had been espoused as another blockbuster anticancer agent.

Single-agent Study (#0141)

In order to assess the effect of cetuximab as a single agent, this study was initiated in early 2001. A total of 57 patients were entered on this study, the results of which were presented[12] at the May 2002 meeting of ASCO. The patients entered had to have "documented progressive disease at any time after receiving an irinotecan-containing regimen." The title of the abstract[12] presented states the patients were refractory to irinotecan, and six patients were stated to have achieved a PR.

The BMS review of the BLA in January 2002 indicates that there was uncertainty regarding the fact that all patients were truly refractory to irinotecan (meaning they had "documented progressive disease") before being entered on the study. The BMS reviewers stated that "irinotecan refractoriness can be inferred" for 11 of the 57 patients, but "the data collected in this trial are insufficient to determine irinotecan refractoriness for any patient." Two of these 11 patients were verified to have had a PR by the BMS review.

Although six patients were stated to have responded to cetuximab given by itself in this study,[12] the BMS review indicates that one of these patients may not truly have had a response. The final opinion of the BMS staff was "there are five patients....whose data compellingly support a determination of partial response to the single agent" cetuximab. Although it is apparent this agent does have some antitumor activity by itself, the rate of such responses, with a solid assessment of the response, is only five (8.7%) of the 57 patients.

Summary

It appears that cetuximab has some antitumor effect for metastatic CRC when used as sole therapy as reported in an ASCO presentation in May this year.[11] Cetuximab also appears to have some effect when given in conjunction with irinotecan despite disease progression having occurred when the patient was treated previously with irinotecan, as was reported at the May 2001 ASCO meeting.[10] However, for some patients it is unclear whether or not the irinotecan makes any contribution to the therapy. The irinotecan perhaps only adds toxicity to the therapy and no benefit. The 9923 study has major problems in adherence to the eligibility criteria and the irinotecan dosing. In addition, the assessments of response are subject to considerable variation depending on who reviews the CT scans. After examining a great deal of the information assembled by the House Committee staff, I agree with the assessment of the three oncologists as published.[9] Based on the results of the 9923 study available for my review, I am unable to determine if this drug has meaningful activity in CRC and adds to patient survival after failure of all available standard therapy. The single-agent study does show the drug has an effect for a rare patient, but a reliable response rate is <10%, a level that possibly provides little patient benefit or improved survival. Unfortunately, further studies will have to be initiated before all these issues are more certain. It is my understanding that BMS and ImClone plan to conduct such further studies.

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(signed) Raymond B. Weiss, MD, FACP 10 June 2002

Mr. GREENWOOD. The Chair thanks our witnesses for your testimony and for your help of this subcommittee with its work and excuses you.

The Chair now calls forward Dr. Samuel Waksal, Ph.D., who is the former chief executive officer of ImClone Systems. Would you please pull the microphone forward very close to you and push the button on it so that it is on.

Mr. SAMUEL WAKSAL. It should be on.

Mr. GREENWOOD. Thank you. Thank you. It is on. Dr. Samuel Waksal is a former ImClone chief executive officer and is here with us today under subpoena. On April 19, 2001, Dr. Waksal did submit to an interview—2002, excuse me—Dr. Waksal did submit to an interview with committee investigators that lasted for about 4 hours. Dr. Waksal was scheduled for another staff interview on May 30 but withdrew from this scheduled interview on advice of counsel. My understanding is that Dr. Waksal authorized his counsel to advise the committee that he will rely on his constitutional right not to testify at today's hearing. I believe that this privilege should be personally exercised before the members of this subcommittee, as we have done in the past, and that is why we have requested Dr. Waksal's appearance today, and I thank you for joining us, sir.

I would urge you, given the importance of your testimony, to reconsider your decision to invoke your Fifth Amendment rights, especially since you may need to amend statements you made earlier to the committee investigators during your interview which, if the Government criminal and civil complaints filed against you yesterday are true, may not be wholly accurate.

Dr. Waksal, you are aware that the committee is holding an investigative hearing, and in doing so we have the practice of taking testimony under oath. Do you have any objection to testifying under oath?

Mr. SAMUEL WAKSAL. No.

Mr. GREENWOOD. The Chair also advises you that under the rules of the House and the rules of the committee, you are entitled to be advised by counsel. Do you desire to be advised by counsel during your testimony today, sir?

Mr. SAMUEL WAKSAL. I have counsel here with me.

Mr. GREENWOOD. Okay. Would you please identify your counsel for the record or your counsel may identify himself.

Mr. LIMAN. Yes. It is Lewis Liman from the law firm Wilmer, Cuttler and Pickering.

Mr. GREENWOOD. Thank you. At this time, Mr. Waksal, if you would stand and raise your right and I will swear you in.

[Witness sworn.]

Mr. GREENWOOD. Okay. Thank you, Dr. Waksal. You are now under oath, and you may give a 5-minute statement for the record if you choose. Do you care to, sir?

TESTIMONY OF SAMUEL WAKSAL, FORMER CHIEF EXECUTIVE OFFICER, IMCLONE SYSTEMS, INC.

Mr. LIMAN. Dr. Waksal will not be giving a statement for the record at this time.

Mr. GREENWOOD. Very well. Then the chairman will recognize himself for questioning of the witness.

Mr. LIMAN. We have submitted a letter to the subcommittee.

Mr. GREENWOOD. Without objection, your letter will be entered into the official record of these proceedings, sir.

Mr. SAMUEL WAKSAL. Thank you.

[The letter follows:]

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June 13, 2002

Honorable James Greenwood
Chairman
Subcommittee on Oversight and
Investigations
Committee on Energy and Commerce
United States House of Representatives
2125 Rayburn House Office Building
Washington, D.C. 20515

Dear Chairman Greenwood:

Last week the Subcommittee served a subpoena on Dr. Samuel

Waksal, formerly the CEO of Imclone Systems, Inc., seeking his testimony before the Subcommittee in connection with a hearing on matters relating to the FDA's consideration of Imclone's submission of a Biologics License Application for Erbitux. Over the last several months, Dr. Waksal has cooperated extensively with the Subcommittee's inquiry by providing a significant number of private documents and meeting with the Subcommittee's staff for an interview.

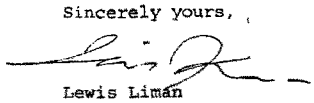
Through late May 2002, Dr. Waksal continued to provide the Subcommittee with information, and had not declined to answer any question put to him or to provide any document requested, notwithstanding that other government agencies were conducting formal investigations concerning the same subject matter.

Yesterday the Department of Justice formally charged Dr. Waksal with violations of securities law and other statutory provisions. Dr. Waksal firmly believes that any allegations against him are unfounded and that he did nothing improper. He also recognizes that this Subcommittee's hearing room is not the constitutionally appropriate venue to resolve those accusations. One of Dr. Waksal's major goals has been to make available a drug that would prolong the lives of people with cancer.

Under these circumstances we, as Dr. Waksal's attorneys, have counseled him to avail himself of the rights provided by the United States Constitution, and respectfully to decline to answer any questions put to him by the Subcommittee at this time.

Dr. Waksal looks forward to being able to refute these allegations in the appropriate forum and then to be able to resume his cooperation with the Subcommittee.

Sincerely yours,



Lewis Liman

Mr. GREENWOOD. Dr. Waksal, on October 29, 2001, you and your brother sold $1.6 million of shares of ImClone to Bristol-Myers Squibb for about $111 million, a sale helped, in part, by all of the hype ImClone generated about its purported wonder drug, Erbitux and made possible, in part, by unsecured loans of about $35 million that you and your brother received from ImClone so you could exercise options to purchase ImClone stock at highly discounted prices. During the same time period, ImClone was running the pivotal clinical trial aimed at supporting an accelerated FDA approval for ImClone's cancer drug, Erbitux. The study turned out to be riddled with severe problems with no apparent quality control by ImClone. As a result, FDA refused to even accept the Erbitux application for filing.

Given the contrast and outcomes, the financial gain of $111 million for you and your brother before the FDA application was even filed and the failure to deliver on your promise to thousands of very sick cancer patients to have Erbitux on the market in spring of 2002, would it be fair to say that your strategy at ImClone was to put personal profiteering ahead of patients, sir?

Mr. SAMUEL WAKSAL. Unfortunately, upon the advice of counsel, I wish to assert my constitutional rights and respectfully decline to answer.

Mr. GREENWOOD. We thank you, sir, and we respect your right to do so. But let me be clear, Dr. Waksal. Are you refusing to answer the question on the basis of the protections afforded to you under the Fifth Amendment to the United States Constitution?

Mr. SAMUEL WAKSAL. Yes.

Mr. GREENWOOD. Dr. Waksal, do you intend to invoke your Fifth Amendment rights in response to any and all questions posed to you here today?

Mr. SAMUEL WAKSAL. Yes.

Mr. GREENWOOD. Okay. Then you are excused from the witness table at this time, but I advise you that you remain subject to the processes of this committee, and that if this committee needs such, then we may recall you, sir.

Mr. SAMUEL WAKSAL. Thank you.

Mr. GREENWOOD. Okay. You are excused, sir.

The Chair then calls forward Dr. Harlan Waksal, M.D., who is now the chief executive officer of ImClone Systems, Inc.; Dr. Laurie Smaldone, M.D., senior vice president, Global Regulatory Sciences for Bristol-Myers Squibb Company. And accompanying Dr. Smaldone is Mr. Brian Markison, vice president, the Division of Oncology at Bristol-Myers Squibb Company.

The Chair welcomes our witnesses. You are both aware, all three of you are aware that this committee is holding an investigative hearing, and it is the practice of this subcommittee to take testimony in such hearings under oath. Do any of you object to giving your testimony under oath this morning?

Mr. HARLAN WAKSAL. No.

Ms. SMALDONE. No.

Mr. GREENWOOD. Okay. It is also the responsibility of the Chair to advise the witnesses that you are entitled to be represented by counsel. Do either of the witnesses choose to be represented by counsel? Dr. Waksal, do you?

Mr. HARLAN WAKSAL. I do have counsel here, sir.

Mr. GREENWOOD. Okay. Your counsel may join you at the table, if he chooses. Would you identify your counsel by name, sir?

Mr. HARLAN WAKSAL. Chip Lowenson.

Mr. GREENWOOD. Would you pull the microphone much closer to yourself, sir, and make sure that it is turned on.

Mr. HARLAN WAKSAL. Is that okay now?

Mr. GREENWOOD. That is perfect, sir. Would you identify your counsel, please?

Mr. HARLAN WAKSAL. Chip Lowenson.

Mr. GREENWOOD. Okay. Dr. Smaldone, do you choose to be represented by counsel?

Ms. SMALDONE. I have my counsel here with me.

Mr. GREENWOOD. You are going to have to do the same thing with your microphone.

Ms. SMALDONE. Sorry. I do have my counsel here with me today.

Mr. GREENWOOD. And would you identify your counsel, ma'am?

Ms. SMALDONE. Evan Chesler.

Mr. GREENWOOD. Pardon me?

Ms. SMALDONE. Evan Chesler.

Mr. GREENWOOD. Okay. If you would then both rise and raise your right hand. Mr. Markison, if you would rise as well and raise your right hand.

[Witnesses sworn.]

Okay. The Chair advises you that you are under oath. And, Dr. Waksal, you are recognized for 5 minutes to provide an opening statement. Do you choose to?

Mr. HARLAN WAKSAL. I do indeed. Thank you.

Mr. GREENWOOD. Please proceed.

TESTIMONY OF HARLAN WAKSAL, CHIEF EXECUTIVE OFFICER, IMCLONE SYSTEMS, INC.; LAURIE SMALDONE, SENIOR VICE PRESIDENT, GLOBAL REGULATORY SCIENCES, BRISTOL-MYERS SQUIBB COMPANY; AND BRIAN MARKISON, VICE PRESIDENT, DIVISION OF ONCOLOGY, BRISTOL-MYERS SQUIBB COMPANY

Mr. HARLAN WAKSAL. Chairman Greenwood, Congressman Deutsch and members of the subcommittee, my name is Harlan Waksal, and I am the President and CEO of ImClone Systems. I have held that position for only 3 weeks, but I have been with the company since it was founded 17 years ago.

Thank you for this opportunity to tell you about Erbitux. Since we licensed this compound 9 years ago, ImClone has invested hundreds of millions of dollars in research and testing Erbitux. Our effort reached a critical point 2 years ago. Doctors at preeminent research centers like Memorial Sloan-Kettering Cancer Center started to report success in using Erbitux in combination with chemotherapy to treat terminally ill patients. These doctors and their patients were telling us that the Erbitux combination therapy was shrinking solid tumors in patients with no other treatment options. So we set out to make this drug available to cancer patients as quickly as possible.

Congress created the Fast Track process to encourage expedited review of drugs that have the potential to address an unmet med-

ical need related to a life-threatening illness. If ever a drug was a good candidate for Fast Track, Erbitux was it. And in fact, the FDA granted Erbitux Fast Track status in January 2001. During this same period, we had many meetings with the FDA to determine whether the clinical trial we had underway for colorectal cancer patients could serve as the basis for regulatory approval. After the FDA reviewed our study protocol, we reached an understanding with the agency that this trial could be the pivotal study for our application.

Over the next few months, we worked closely with the FDA to develop an application for approval. When the FDA asked questions, we answered them. When the FDA asked for more data, we got it for them. Such give and take is a common part of the application process. We were very pleased with the results of the clinical trial. It found that roughly 20 percent of patients responded to that treatment. These results were reported by independent physicians at preeminent cancer centers—doctors with no stake in the outcome, who saw the drug at work, first hand, in their patients. These conclusions were then confirmed by an independent committee, known as an IRAC. Twenty percent was an impressive result, since the FDA had approved Irinotecan, a chemotherapy drug, with a 13 percent response rate.

But we were not the only ones excited by the potential of Erbitux. In May 2001, doctors at the leading oncology conference reacted enthusiastic to the data presented by Dr. Leonard Saltz on the Erbitux trial. And in September of last year, after months of due diligence by their top scientists, Bristol-Myers Squibb committed to invest $2 billion in ImClone, a huge vote of confidence for Erbitux from the world's leading cancer drug company.

Despite these encouraging signs, the FDA refused to file ImClone's application. Today, this hearing will be filled with questions as to why the FDA refused to file our application, and I am happy to answer those questions. But in brief, let me say that with the benefit of 20/20 hindsight, we could and should have done a better job in documenting the clinical evidence. Many of our critics have suggested that the pilot trial was too small and that our results were not proven by the most rigorous testing standards. But I would remind those critics that Congress explicitly created Fast Track to bring drugs to market that had not been through the rigors of a Phase III test, wisely deciding that when patients are dying and drugs demonstrate potential for treating them, the balance should be struck in favor of getting those drugs to patients quickly.

Today, ImClone and its partners continue to work closely with the FDA to move forward in the approval process. Erbitux remains on the FDA's Fast Track. We will be submitting new data as it comes in and still hope to win accelerated approval. We also have other clinical tests underway, including large Phase III trials.

Mr. Chairman, in conclusion, I would like to make two points. First, while we had the right intentions in trying to get Erbitux through the filing process in 2001, we failed. Yes, setbacks in regulatory strategies occur, in fact they are common, and ImClone is hardly among the only biopharmaceutical or pharmaceutical companies that have failed in gaining swift approval for a drug. But

that does not change the fact that we let patients down, and for that, I am truly sorry.

Second, as the company's new CEO, I am committed, absolutely committed, to getting this drug approved. I will work closely with the FDA and try to continue the cooperative relationship we have had with the agency. We want to get them the information they need as quickly as we can so that hopefully Erbitux can be available to cancer patients in desperate need of more treatments.

I appreciate the opportunity to be here today to answer your questions.

[The prepared statement of Harlan Waksal follows:]

PREPARED STATEMENT OF HARLAN WAKSAL, PRESIDENT AND CHIEF EXECUTIVE OFFICER, IMCLONE SYSTEMS

Chairman Greenwood, Congressman Deutsch and Members of the Subcommittee, my name is Harlan Waksal, and I am the President and Chief Executive Officer of ImClone Systems. I have held that position for only three weeks, but I have been with the company since it was founded, 17 years ago.

Thank you for this opportunity to tell you about Erbitux—a potential new treatment for cancer that attaches itself to growth factor receptors on cancer cells, depriving tumors of the ability to grow. Since we acquired the license for this compound nine years ago, ImClone has invested hundreds of millions of dollars to support its clinical program of research and testing.

Our efforts reached a critical point two years ago. Over the course of the year 2000, doctors at preeminent research institutes such as the Memorial Sloan-Kettering Cancer Center reported success in using Erbitux in combination with chemotherapy to treat terminally ill patients. These doctors—and their patients—were telling us that the Erbitux combination therapy was shrinking solid tumors in patients who did not have other treatment options. As a result, we set out to make this drug available to cancer patients as quickly as possible.

As this Subcommittee knows, Congress created the "Fast Track" process to encourage the expedited review of drug applications where the drug in question has the potential to address an unmet medical need related to a life-threatening illness. If ever a drug was a good candidate for "Fast Track," Erbitux was it. And in fact, the FDA granted Erbitux "Fast Track" status in January 2001.

During this same period, we had multiple meetings and conversations with the FDA, to determine whether the clinical trial we had underway for colorectal cancer patients—giving Erbitux and chemotherapy in combination to patients who had failed chemotherapy alone—could serve as the basis for regulatory approval. After the FDA reviewed our test protocol, we reached an understanding with the agency that this clinical study could be the pivotal study for our application to win approval for Erbitux.

Over the next few months, we worked closely with the FDA to develop an application for approval. When the FDA asked questions, we answered them. When the FDA asked for more data, we got it for them. Such give and take is a common part of the application process.

We were very pleased with the results of the clinical trial. It found that roughly 20 percent of patients responded to the treatment. These results were reported by independent physicians at preeminent cancer centers—doctors without any stake in the outcome, who saw this drug at work, first hand, in their patients. These conclusions were then confirmed by an independent review committee, commonly known as an "IRAC." The approximately 20% response rate was an impressive result, since the FDA had approved irinotecan—a chemotherapy drug—with a 13% response rate in a similar patient population.

But we were not the only people excited by the potential of Erbitux. In May of 2001, doctors at the leading oncology conference—after hearing a presentation from Dr. Leonard Saltz regarding the clinical trial—reacted enthusiastically to the data. And in September of last year, after months of extensive due diligence by their top scientists, Bristol-Myers Squibb committed to investing $2 billion in ImClone and Erbitux—a huge vote of confidence from the world's leading oncology pharmaceutical company, which clearly believed that Erbitux showed great potential.

As the Subcommittee knows, despite these encouraging signs, the FDA refused to file ImClone's application for Erbitux. Today's hearing will be filled with questions as to why the FDA refused to file our application, which I am happy to answer. But

in brief, let me say that with the benefit of 20/20 hindsight, we now know that we could and should have done a better job in putting together our application package.

Many of our critics have suggested that our pivotal trial was too small, and that our results were not proven by the most rigorous testing standards. But, I would remind those critics that Congress explicitly created Fast Track to bring drugs to market that had not been through the rigors of a Phase III test—wisely deciding that when patients are dying, and there is a drug that demonstrates "potential" for treating those patients, the balance should be struck toward getting new drugs to those patients quickly.

Notwithstanding our setbacks, ImClone and its partners continue to work closely with the FDA to move forward in the approval process. Today, Erbitux remains on the FDA's "Fast Track." We will be submitting new data as it comes in, and still hope to win accelerated approval. We also have underway a variety of other clinical tests, including large, Phase III trials.

Mr. Chairman, in conclusion, I would like to make two points.

First, while we had the right intentions in trying to get Erbitux through the filing process in 2001, we failed. Yes, setbacks in the regulatory process are common, and ImClone is hardly alone among drug companies in failing to win swift approval for a drug. But that does not change the fact that we let patients down, and for that, I am truly sorry.

Second, as ImClone's new CEO, I am committed—absolutely committed—to getting this drug approved. I will work closely with patients and the advocacy community to see this through. And I will also work closely with the FDA, to continue the open and cooperative relationship we have had with the agency. We want to get them the information they need, as quickly as we can, so that hopefully Erbitux can be available to cancer patients in desperate need of more treatment options.

I appreciate the opportunity to be here today, and will be glad to answer your questions now.

Mr. GREENWOOD. The Chair thanks you, Dr. Waksal, for your statement. The Chair also thanks you for your presence and your willingness to come here without subpoena. And let me personally say that I certainly hope that you succeed in having this drug approved if it will in fact help patients.

Dr. Smaldone, you are recognized to give your opening statement for 5 minutes, please.

TESTIMONY OF LAURIE SMALDONE

Ms. SMALDONE. Yes, thank you. Thank you, Mr. Chairman and thanks to the committee. My name is Laurie Smaldone, and I am senior vice president of Worldwide Regulatory Science at the Bristol-Myers Squibb Pharmaceutical Research Institute, and a physician specializing in oncology. I have been with Bristol-Myers Squibb for 17 years, and before that I was an oncologist in academic practice. While the scope of my responsibilities at Bristol-Myers Squibb today crosses therapeutic lines, a great deal of my professional experience has been in the area of cancer and, more specifically, cancer treatments.

I am pleased to have the opportunity to address the subcommittee, as well as respond to its questions, about Bristol-Myers Squibb's commitment to the anti-cancer drug, Erbitux. First, I would like to say that from a scientific and clinical perspective, we believe that Erbitux is an active anti-cancer agent. Evidence suggests that Erbitux shows anti-tumor activity in several tumor types but in particular in patients with late-stage colorectal cancer that is refractory, or, in other words, unresponsive to available treatments. These are patients who otherwise have few if any treatment options available to them. We believe this about Erbitux now, just as we believed it when we invested in ImClone Systems and en-

tered into a commercialization agreement with ImClone relating to Erbitux back in September 2001.

It is important for the subcommittee to understand that one of the diseases for which Erbitux is being investigated as a possible treatment, advanced refractory colorectal cancer, is particularly insidious. For individuals diagnosed with it, the prognosis is uniformly grim; this is an incurable disease. Still, many patients are desperate for any treatment that will give them additional time with family and loved ones, and in some cases, Erbitux has helped provide this additional time.

While the difficulties in finding adequate treatments for cancer are well known, it is useful to point out that great progress has been made in understanding the course and complexities of cancer over the last many years. Nonetheless, beyond early detection and surgical intervention, major impact with chemotherapy and biologic therapies is limited, and still most tumors go undetected until quite an advanced stage, which makes any treatment effect at that time far more difficult to achieve.

As the world's leading provider of cancer therapies, Bristol-Myers Squibb has focused much of its research and development on finding better treatments, more targeted and less toxic therapies than those currently available. And our strategy also has been to look outside our company for promising compounds such as Erbitux, which itself represents a new and potentially revolutionary way of fighting cancer through a more targeted approach. Still, we realize that these advances, while significant, are not the "magic bullet" against cancer, but they do represent real progress.

My second point is that it is important, in the midst of all the issues identified, that we together find a way to address these issues and make Erbitux available to patients as quickly as possible. That is why we continue to work closely with ImClone to further the development of Erbitux and to resubmit the application to the U.S. Food and Drug Administration as soon as possible. While some patients have been able to benefit from Erbitux in clinical trials and compassionate use programs, we know that only after approval and commercialization will all those who truly need the drug actually get it and will physicians be able to further evaluate its role in different settings.

Finally, I wish to stress that this is about everyday people, more than 100,000 each year, who 1 day go to their doctor and have their entire life turned upside down by a diagnosis of colon cancer. For these people, Erbitux is not an exciting scientific advance or a compelling idea or a promising investment. It is a treatment option and a way to have more time and hope. I can say this with some conviction because I had the honor recently of meeting an Erbitux patient who told me quite candidly what the drug has meant to her. And she has permitted me to share her story with the committee, which I will do very briefly.

A little over a year ago, when she was 38 years old, Michael Ann Mullinix of Belvidere, Illinois, was told by her doctor that she had stage 4 metastatic colon cancer that had spread to her ovaries. Even with surgery, she was given a short time to live. A wife and a mother of teenage children, Michael Ann decided she wanted to go on an Erbitux regimen. Following surgery, she began treatment

with Erbitux and other chemotherapeutic agents last August as part of a clinical study. And as of today, she is essentially cancer free and continues to respond.

In the course of our conversation, Michael Ann told me that she was worried not that her cancer would return, or how she was coping with this serious illness. She was worried about the future of Erbitux, about its continued availability as a therapy alternative, not just for her benefit but for many others who could potentially benefit as well. When she heard that I was coming to testify before this subcommittee, she asked me to convey this message that I have stressed in this statement: We need to work together to do all that we can to get Erbitux to all the patients who need it as quickly as possible.

I should point out that there are risks involved in this project, just as there are risks involved in all of biomedical research. We have no guarantee that Erbitux ultimately will be the important therapeutic advance we expect it to be. But knowing what we know about it today, there is every reason to be hopeful about its promise and to move forward with the clinical development and registration process.

Once again, I am grateful for the opportunity to address the committee on this important subject. I will be happy now to answer any questions you have.

[The prepared statement of Laurie Smaldone follows:]

PREPARED STATEMENT OF LAURIE SMALDONE, SENIOR VICE PRESIDENT, WORLDWIDE REGULATORY SCIENCE, BRISTOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE

Thank you, Mr. Chairman. My name is Laurie Smaldone, and I am senior vice president of Worldwide Regulatory Science at the Bristol-Myers Squibb Pharmaceutical Research Institute, and a physician specializing in oncology. I have been with Bristol-Myers Squibb for 17 years, and before that I was an oncologist in academic practice. While the scope of my responsibilities at Bristol-Myers Squibb crosses therapeutic lines, a great deal of my professional experience has been in the area of cancer and, more specifically, cancer treatments.

I am pleased to have this opportunity to address the subcommittee, as well as respond to its questions, about Bristol-Myers Squibb's commitment to the anti-cancer agent Erbitux. First, I would like to say that—from a scientific and clinical perspective—we believe that Erbitux is an active anti-cancer agent. Evidence suggests that Erbitux shows anti-tumor activity in patients with late-stage colorectal cancer that is refractory—or, in other words, unresponsive—to available treatments. These are patients who otherwise have few if any treatment options available to them. We believe this about Erbitux now, just as we believed it when we invested in ImClone Systems and entered into a commercialization arrangement with ImClone relating to Erbitux back in September 2001.

It is important for the subcommittee to understand that the disease for which Erbitux is being investigated as a possible treatment—advanced refractory colorectal cancer—is particularly insidious. For individuals diagnosed with it, the prognosis is generally grim. Still, many patients are desperate for any treatment that will give them additional time with family and other loved ones. And in some cases, Erbitux has helped provide this additional time.

While the difficulties in finding adequate treatments for cancer are well known, it is useful to point out that great progress has been made in understanding the course and complexities of cancer. Nonetheless, beyond early detection and surgical intervention, major impact with chemotherapy and biologic therapies is limited, and still most tumors go undetected until quite an advanced stage.

As the world's leading provider of cancer therapies, Bristol-Myers Squibb has focused much of its research and development on finding better treatments—more targeted and less toxic therapies than those currently available. And our strategy also has been to look outside our company for promising compounds such as Erbitux, which itself represents a new and potentially revolutionary way of fighting cancer

through a more targeted approach. Still, we realize that these advances—while significant—are not the "magic bullet" against cancer, but they represent real progress.

My second point is that it is important—in the midst of all the issues identified—that we together find a way to address these issues and make Erbitux available to patients as quickly as possible. That is why we are working closely with ImClone to resubmit the application for Erbitux to the U.S. Food and Drug Administration as soon as possible. While some patients have been able to benefit from Erbitux in clinical trials and compassionate use programs, we know that only after approval and commercialization will all those who truly need the drug actually get it, and will physicians be able to further evaluate its role in different clinical settings.

Finally, I wish to stress that this is about everyday people from all walks of life—thousands of them each year—who one day go to their doctor or to the hospital and have their entire life turned upside down by a diagnosis of colon cancer or other solid tumors. For these people, Erbitux is not an exciting scientific advance or a compelling idea or a promising investment. It's a way to have more time.

I can say this with some conviction because I had the honor recently of meeting an Erbitux patient who told me quite candidly what the drug has meant to her. And she has permitted me to share her story with the committee, which I will do now, briefly.

A little over a year ago, when she was 38 years old, Michael Ann Mullinix of Belvidere, Illinois, was told by her doctor that she had stage 4 colon cancer that had spread to her ovaries. Even with surgery, she was given just 9 months to live. A wife and a mother of teenage children, Michael Ann decided she was going to fight the odds by going on an Erbitux regimen, which she had heard about on television. Following surgery, she began treatment with Erbitux and other chemotherapeutic agents last August as part of a clinical study. And as of today, she is essentially cancer free.

In the course of our conversation, Michael Ann told me that she was worried. Not that her cancer would return, or how she was coping with this serious illness. She was worried about the future of Erbitux—about its continued availability as a therapy alternative, not just for her benefit but for many others who would potentially benefit from it as well. And when she heard that I was coming to testify before this subcommittee, she asked me to convey the message I have stressed several times in this statement: we need to work together to do all we can to get Erbitux to all the patients who need it as quickly as possible.

I should point out that there are risks involved in this project, just as there are risks in all biomedical research. We have no guarantee that Erbitux ultimately will be the important therapeutic advance we expect it to be. But knowing what we know about it today, there is every reason to be hopeful about its promise and to move forward with the clinical development and registration process.

Once again, I am grateful for this opportunity to address the committee on this important subject. I'll be happy now to answer any questions you may have.

Mr. GREENWOOD. Thank you, Dr. Smaldone. We appreciate your presence and your testimony.

Ms. SMALDONE. Thank you.

Mr. GREENWOOD. The Chair recognizes himself for 5 minutes for purposes of inquiry. Let me address my questions initially to Dr. Waksal. When ImClone filed the Erbitux biologics licensing application, otherwise known as a BLA, on October 31, 2001, did you expect that ImClone was in fact on a glide path toward approval?

Mr. HARLAN WAKSAL. Absolutely. We did file it at that time. In fact, it was a rolling BLA. That was the last piece of it. We thought we were well on the track to moving this drug through approval.

Mr. GREENWOOD. And did you expect that Erbitux BLA to go before the February 2002 FDA Advisory Committee called ODAC?

Mr. HARLAN WAKSAL. Well, we were hopeful that based on timing of the review clock that the February ODAC would be the appropriate time for this drug to be in front of the Oncologic Drug Advisory Committee.

Mr. GREENWOOD. Okay. Does Lilly Lee, ImClone's Regulatory Affairs vice president report directly to you?

Mr. HARLAN WAKSAL. Yes, she does.

Mr. GREENWOOD. And was she reporting to you her contacts and communications with FDA during the approval process?

Mr. HARLAN WAKSAL. Yes, she was.

Mr. GREENWOOD. Okay. Dr. Lee, could you please come forward to be sworn in and answer a few questions? Welcome, Dr. Lee. You may be seated for a moment and then we will ask you to stand again. You have heard me say, Dr. Lee, that this is an investigative hearing, and it is our practice to take testimony under oath. Do you have any objections to giving your testimony to us under oath?

Ms. LEE. No.

Mr. GREENWOOD. Okay. You also should be advised that you are entitled to counsel. Do you wish to be advised by counsel?

Ms. LEE. Yes, please.

Mr. GREENWOOD. Okay. And could you identify your counsel for us, please?

Ms. LEE. Mr. Richard Emory.

Mr. GREENWOOD. Mr. Richard Emory?

Ms. LEE. Yes.

Mr. GREENWOOD. Okay. Thank you. In that case, would you now rise and raise your right hand?

Ms. LEE. Sure.

[Witness sworn.]

Mr. GREENWOOD. Thank you, Dr. Lee. Did you have a face-to-face meeting with the FDA reviewers on December 4, 2001?

Ms. LEE. Yes, I did.

Mr. GREENWOOD. Okay. Did the FDA reviewers raise serious questions about the documentation of the study at that time?

Ms. LEE. They had raised questions about the documentation.

Mr. GREENWOOD. Okay. Did you ask the FDA reviewers whether the FDA was going to send ImClone a refusal-to-file letter?

Ms. LEE. No, I did not ask that.

Mr. GREENWOOD. Okay. Did it come up in the conversation? Was there any discussion of the possibility of a refusal-to-file letter?

Ms. LEE. The only mention of a refusal-to-file was in the context of the FDA reviewer laying out the next steps, and it was one of the three possible outcomes after the would have the internal filing meeting. The three outcomes that he had laid out is, one, the FDA could accept and review; two, since this was a rolling submission, ImClone may decide that the last piece was actually not the last piece that complete the BLA; and three, is the FDA may issue a refusal-to-file, RTF. So these three options are really any drug that filed an application, any BLA would face those three same scenarios.

Mr. GREENWOOD. Did you not tell our committee staff in your interview that after your conversation an RTF letter for the first time became a possibility in your mind?

Ms. LEE. For me it was on December 13 that the possibility that the review—issues that we were working on with the FDA may lead to an RTF.

Mr. GREENWOOD. Okay. Let me turn back to you, Dr. Waksal.

Mr. HARLAN WAKSAL. Yes, sir.

Mr. GREENWOOD. Do you recall Dr. Lee telling you about this meeting?

Mr. HARLAN WAKSAL. Yes, she did.

Mr. GREENWOOD. And were you aware of the FDA issues at this point in time, what their concerns were?

Mr. HARLAN WAKSAL. Yes. Dr. Lee articulated very clearly the issues, the documentation questions that were being raised by the FDA.

Mr. GREENWOOD. Weren't the nature of these issues—when did that happen?

Mr. HARLAN WAKSAL. We spoke many times, but December 4 was—you are referring to the December 4 meeting, so it was in the afternoon on December 4.

Mr. GREENWOOD. Okay. Weren't the nature of these issues such that it was obvious that whether FDA refused to file or not, ImClone wasn't going to the February 2002 Advisory Panel?

Mr. HARLAN WAKSAL. No, not at all. At the time, we felt very confident about our ability to go ahead and address those issues. In fact, we were putting into place a plan to go ahead and make sure that we could address the FDA's concerns and issues that were being raised and felt that indeed we could go ahead and continue to move this drug forward.

Mr. GREENWOOD. And be ready for the February Advisory Panel.

Mr. HARLAN WAKSAL. Well, the preparation for any advisory committee is not dependent on the company, it is dependent on the FDA and their feeling that they are ready in fact to go ahead and present it and move it forward. We don't really have control over that. Obviously, it is always our hope to get it to an advisory committee as quickly as possible.

Mr. GREENWOOD. December 4 was also an important date for another reason. Wasn't that the date that ImClone filed the rest of the single agent study?

Mr. HARLAN WAKSAL. That is right. In fact, the real purpose of the meeting, why the meeting took place, was we were delivering the last portion of the package to the FDA, and that was the final results, the final study report on the single agent trial on 57 patients.

Mr. GREENWOOD. And were the results of the single agent study a factor cited in the FDA refusal-to-file letter?

Mr. HARLAN WAKSAL. Yes, it was.

Mr. GREENWOOD. According to public records, you gained almost $50 million from a carry-forward stock transaction on December 6, 2001; is that correct?

Mr. HARLAN WAKSAL. That is correct.

Mr. GREENWOOD. This is the transaction you said in an October 31, 2001 letter to the ImClone Board that you would execute in 2 weeks, and on December 6, ImClone was trading near its 52-week peak price. Dr. Waksal, did you not have important non-public information about the status of the Erbitux application when you executed the December 6 sale of ImClone stock for almost $50 million?

Mr. HARLAN WAKSAL. That is correct. There was no material information, in my opinion, at the time. In fact, my transaction was quite independent of everything else taking place. That transaction was one that I defined and identified months earlier, identified the board of directors on October 31, and these are complicated trans-

actions, and it took until the beginning of December for it to be finalized. Before the December 4 meeting, I, in fact, had already transferred the stock and had engaged in that effort, but the event on December 4 was not a material event. We didn't believe it would be——

Mr. GREENWOOD. But it was non-public.

Mr. HARLAN WAKSAL. Pardon me?

Mr. GREENWOOD. It was not public, though.

Mr. HARLAN WAKSAL. No, it was not public, but there was no material information——

Mr. GREENWOOD. Your argument is that while it was non-public, it was not material.

Mr. HARLAN WAKSAL. That is correct, sir.

Mr. GREENWOOD. Okay. My time has expired. The Chair recognizes the gentleman, Mr. Stupak, for 5 minutes.

Mr. STUPAK. Thank you. Dr. Waksal, in August 2000, when you met with the FDA, were you present at that meeting?

Mr. HARLAN WAKSAL. I was.

Mr. STUPAK. Okay. And who set up the protocol that you would use to get this Fast Tracked?

Mr. HARLAN WAKSAL. The protocol was set up by a variety of people. We generally work with a group of oncology consultants, the people who are going ahead and doing the trial, in conjunction with our in-house people who are responsible for writing it. It goes through review committees and we get feedback till we get to the final form.

Mr. STUPAK. But, basically, ImClone sets forth the protocol.

Mr. HARLAN WAKSAL. That is correct, ImClone is responsible for the protocol.

Mr. STUPAK. And that is what you were presenting to the FDA in August of 2000 and hoped to get to Fast Track.

Mr. HARLAN WAKSAL. That is right.

Mr. STUPAK. And, actually, on January 12, 2001, you did receive the Fast Track authority from FDA to proceed.

Mr. HARLAN WAKSAL. That is correct.

Mr. STUPAK. And there is some question as to what protocol was being used, protocol No. 1 or protocol No. 2; is that correct?

Mr. HARLAN WAKSAL. That is not correct.

Mr. STUPAK. Well, in the letter of January 19, from FDA, where they laid it out for you what you were supposed to be doing with the—and also that there would have to be a small study of the single data, was that news to you or——

Mr. HARLAN WAKSAL. Well, that was the first time that was mentioned. But just to get back to the first question, the FDA had both protocols, and it wasn't as if there were two protocols.

Mr. STUPAK. You presented two protocols in August 2000?

Mr. HARLAN WAKSAL. We presented two protocols well before August 2000.

Mr. STUPAK. Okay.

Mr. HARLAN WAKSAL. The protocol was amended, so it was slightly modified, and the FDA had both protocols in their hands while this study was underway, without any question, sir.

Mr. STUPAK. But when you met with them in August 2000——

Mr. HARLAN WAKSAL. Yes. We were talking about the protocols——

Mr. STUPAK. You had both protocols.

Mr. HARLAN WAKSAL. Yes, the FDA had both protocols.

Mr. STUPAK. And it was clear to everyone that there were two protocols here and it is clear to everybody?

Mr. HARLAN WAKSAL. There was never an issue or suggestion that that was a problem in any way. The protocol modifications were minor.

Mr. STUPAK. They were minor?

Mr. HARLAN WAKSAL. Yes, sir.

Mr. STUPAK. Who sets the modifications of the protocol?

Mr. HARLAN WAKSAL. It is usually done in conjunction—again, ImClone sets them in conjunction with the oncologists when they believe there is a change that is necessary in a protocol.

Mr. STUPAK. But Dr. Weiss had just testified that the dosage and the amount of—and the time of receiving some of the drugs, the——

Mr. HARLAN WAKSAL. Irinotecan.

Mr. STUPAK. [continuing] Irinotecan——

Mr. HARLAN WAKSAL. Yes.

Mr. STUPAK. [continuing] that was determined by the doctors doing the testing on the patients, correct?

Mr. HARLAN WAKSAL. Well, actually, the protocol set out very clearly what should take place with Irinotecan treatment. There were protocol deviations that took place where doctors had gone ahead and made changes in that dose of Irinotecan, primarily decreasing the amount of Irinotecan that was being used in those patients. In a very few number of patients, very few, it was increased. And in fact only one of those patients has responded.

Mr. STUPAK. But those modifications were fatal to your application, were they not, one of the three reasons why your application failed.

Mr. HARLAN WAKSAL. I think the application failed for a number of reasons, primarily documentation. But I think that certainly the review——

Mr. STUPAK. Wait a minute. Documentation? You had to have had at least 100 people go through this thing. In the final analysis, there is maybe 89 at best. That is not a documentation issue, that is a fact issue that you didn't have enough people in your small study. And when you have a small study, as been testified earlier, it is critical that everyone makes it through and you do not fall below that 100 number; isn't that correct?

Mr. HARLAN WAKSAL. That is not correct, and if I could——

Mr. STUPAK. That is not correct? Dr. Weiss was wrong in his testimony earlier today?

Mr. HARLAN WAKSAL. I didn't hear Dr. Weiss' testimony, but if I could just go ahead and comment on this.

Mr. STUPAK. Sure. Well, I don't want you to filibuster an answer, I just want an answer.

Mr. HARLAN WAKSAL. I have no intention of filibustering.

Mr. STUPAK. Okay.

Mr. HARLAN WAKSAL. The study was 138 patients. One hundred and twenty of those patients were considered refractory.

Mr. STUPAK. Correct.

Mr. HARLAN WAKSAL. The documentation is not on patients on study, it has to do with patients before they came on to trial, and in fact——

Mr. STUPAK. Doctor, if it is just a matter of documentation, just a matter of documentation and not the size of study and not when dosage is, as you say, it is just documentation, why haven't you provided the proper documentation into the FDA and get this drug approved?

Mr. HARLAN WAKSAL. We, at the time, didn't recognize that there was a shortcoming in the documentation, and that was a quality problem within our company, and it is something that I have agreed was a problem. We have since gone out and have collected with our partners as many scans as we can, collected 133 of the 138 patient scans. They haven't been reviewed yet. We are waiting and talking to the agency, and it will be a component, hopefully, of a resubmission in conjunction with additional data.

Mr. STUPAK. So you are still under the impression it is just a documentation issue and that is all it is. And once that documentation is provided, you expect to get your approval?

Mr. HARLAN WAKSAL. In no way am I trivializing the importance of this documentation. It is critical to the study and its integrity. And not only is that important but the other issues that you have raised are important as well. But the real issue is the question of whether or not these are major or minor deviations or protocol problems. And for the most part, our review continues to establish that the vast majority are not major protocol problems and in fact the study hopefully will continue to be in tact once we reevaluate it. That has not taken place yet. But it is more than documentation, without a question.

Mr. STUPAK. You know, some of the documents we have here indicating that three prominent oncologists say, and let me quote, "Overall, this is a protocol," NCR protocol, right?

Mr. HARLAN WAKSAL. Yes, sir.

Mr. STUPAK. "That asks the wrong questions and then is not tightly written and efficient. The protocol generates far more questions than it could ever answer. It is a blueprint for production of vague answers."

Mr. HARLAN WAKSAL. I believe you are reading from the Cancer Letter, three clinicians who reviewed the protocol, who were not involved with the study or the study design. I think what is very critical in this study was——

Mr. STUPAK. So your answer is only those doctors who were involved in the study can answer or review your BLA?

Mr. HARLAN WAKSAL. No, not at all. No. I believe the importance of how we got to this place is very critical, and unfortunately those physicians weren't involved in that process. What is critical is that this study was not designed as a registration trial. It was a Phase II study early on in the development of this drug. It was only because of the unexpected results that we were able to go ahead and move it forward, sir.

Mr. STUPAK. It is no longer a Phase II study. You are asking for accelerated Fast Track to put it out to the general population. You are past Phase II. We call it Phase III, and Phase IV is when you

put it out in the real world. Therefore, if it is only Phase II, you still had two more phases to go through if you went through the regular process.

Mr. HARLAN WAKSAL. Actually, it was Congress who stipulated in Fast Track designation——

Mr. STUPAK. That is true.

Mr. HARLAN WAKSAL. [continuing] that studies exactly like this could be designated to be moved forward toward approval.

Mr. STUPAK. Exactly.

Mr. HARLAN WAKSAL. Phase II studies, sir.

Mr. STUPAK. And Congress also said that if you are going to do a Fast Track legislation, it has to be tightly controlled, tightly regulated, and you must follow the regimen to a tee; otherwise, we are not going to allow it.

Mr. HARLAN WAKSAL. And we have agreed that there were problems in the protocol.

Mr. GREENWOOD. Time of the gentleman has expired. The Chair recognizes the chairman of the full committee, Mr. Tauzin, for inquiry.

Chairman TAUZIN. Thank you, Mr. Chairman. Gentlemen, let me take you back to December 20. Are you aware of the fact that the FDA called both ImClone and I think Bristol-Myers Squibb on that date to say, "The decision has been made. Don't call us, don't bother us anymore. We will announce the decision on December 28." Is that correct?

Mr. HARLAN WAKSAL. Well, Congressman, what took place is we actually had called the FDA to find out what the status was, and we were informed at the time that a decision had been made and that it would be coming sometime the next week, right.

Chairman TAUZIN. Is that correct, Mr. Markison?

Mr. MARKISON. That is correct.

Chairman TAUZIN. Turn your mike on please, sir. Is that correct?

Mr. MARKISON. Yes, that is correct.

Chairman TAUZIN. Did you get a call from FDA saying, "Don't call, don't bother us anymore. We are going to have the decision—it is already made, we will announce it next week on the 28th."

Mr. MARKISON. Was that question directed to me or Dr. Waksal?

Chairman TAUZIN. Yes, sir. Directed to you, sir.

Mr. MARKISON. I never received a call from the FDA.

Chairman TAUZIN. Did you know that FDA had called ImClone?

Mr. MARKISON. I was aware of the teleconference that Dr. Waksal referred to. And I was aware subsequently of a dialog around that within both companies, and we acknowledged the fact——

Chairman TAUZIN. All right.

Mr. MARKISON. [continuing] that that was a very difficult call.

Chairman TAUZIN. Now, on December 21, Christmas day, you tracked Dr. Waksal down to talk to him. Where did you find him?

Mr. MARKISON. Well, sir, first I must apologize to the chairman as well, I am also represented by counsel. I wasn't asked to point that out. I feel that I should point that out.

Mr. GREENWOOD. Please identify your counsel.

Mr. MARKISON. Mr. Hamilton, behind me.

Mr. GREENWOOD. All right. Say his name clearly in the microphone, please. State his name.

Mr. MARKISON. Mr. James Hamilton.

Mr. GREENWOOD. Okay.

Mr. MARKISON. The only reason I didn't offer his name, I wasn't asked previously, sir.

Mr. GREENWOOD. Fair enough.

Chairman TAUZIN. All right. We got your counsel on the record. Now, let us see if we can get the question answered. The question is on December 25 you apparently tracked down Dr. Waksal by phone to have a conversation with him, Christmas Day, December 25. Where did you find him?

Mr. MARKISON. I was able to reach Dr. Waksal at his house in Telluride.

Chairman TAUZIN. That is in Colorado?

Mr. MARKISON. I believe so, yes.

Chairman TAUZIN. So what was the purpose, why were you calling him on Christmas Day at his house in Colorado?

Mr. MARKISON. The reason I called Dr. Waksal was because on Christmas Eve I had heard from outside counsel to BMS, Mr. Allan Bennett, that through a contact at the FDA we had heard that a refusal-to-file letter was a distinct possibility. And then I tried to reach Dr. Waksal that evening, called his home, but did not leave a message on his machine and then called him on Christmas Day to relay that information.

Chairman TAUZIN. All right. Now, Dr. Waksal, you tried to reach your brother the next morning, you called him three times, I think, starting at 6:30 a.m.; is that correct?

Mr. HARLAN WAKSAL. In fact, I called many members of ImClone senior management, including Sam. I was unable to reach him.

Chairman TAUZIN. Where was he?

Mr. HARLAN WAKSAL. I believe he was somewhere—he was on vacation down in the Caribbean. I don't know——

Chairman TAUZIN. St. Barts, you think.

Mr. HARLAN WAKSAL. That may be correct.

Chairman TAUZIN. And why were you trying to call him?

Mr. HARLAN WAKSAL. I had just heard from our colleagues at Bristol-Myers that we had a refusal—a high potential, a high likelihood of receiving a refusal-to-file, and I was calling all the senior members of management to participate in a conference call that was scheduled for 10 a.m. eastern time where we could discuss our options.

Chairman TAUZIN. Now, for the record, both of you are testifying that the most you got from this contact with a consultant who had a contact with somebody at FDA that a refusal-to-file letter was probable, likely? What did you hear exactly, Mr. Markison?

Mr. MARKISON. I had a dialog with Mr. Bennett where he described that a refusal-to-file letter was probabilistic, highly probable. And then, subsequently, in an e-mail to me, he did point out, in no uncertain terms, that a refusal-to-file letter would be coming.

Chairman TAUZIN. No, no, wait a minute. So when did you get that e-mail?

Mr. MARKISON. On Christmas Eve.

Chairman TAUZIN. So before you called Dr. Waksal, you already had an e-mail saying that a refusal-to-file is coming definitely.

Mr. MARKISON. Yes, sir.

Chairman TAUZIN. Did you convey that information to Dr. Waksal on Christmas Day?

Mr. MARKISON. I conveyed the information that was in the e-mail and also my subsequent dialog with Mr. Bennett that it appeared a refusal-to-letter was coming.

Chairman TAUZIN. Now, Dr. Waksal, you just said you were conveying the message to everyone that that was a problem. Are you telling us that you did not convey to your officers and directors and try to convey to your brother the fact that an e-mail had been received saying one was definitely coming?

Mr. HARLAN WAKSAL. No, I didn't say that at all. I was——

Chairman TAUZIN. Tell me what you did convey.

Mr. HARLAN WAKSAL. I was very clear. I relayed the conversation I had with Mr. Markison to the team. I asked them all to participate so that we could hear directly from the people involved what was going to take place, and in fact we had that telephone conference call with all parties at 10 a.m. on the 26th.

Chairman TAUZIN. On the 26th.

Mr. HARLAN WAKSAL. That is correct.

Chairman TAUZIN. So that by the 25th you all knew that in fact a letter, the refusal-to-file decision had been made and it was going to be announced; is that right?

Mr. HARLAN WAKSAL. Actually, I don't know who knew on Bristol's side. I was the only person who knew on the 25th, and I did not contact anyone on the 25th of December. I didn't feel it was appropriate to wreck Christmas for the people at the company.

Chairman TAUZIN. Now, I have got in my hands a document marked, "Confidential treatment requested by ImClone Systems, Inc." We are going to make a copy available to you, Dr. Waksal.

Mr. HARLAN WAKSAL. Thank you.

Chairman TAUZIN. It is a series of memos, handwritten memos. We don't know who wrote it, but the date on top, if you will follow it, is December 27, 2001; is that correct?

Mr. HARLAN WAKSAL. That is correct, sir.

Chairman TAUZIN. Would you read the second item for us?

Mr. HARLAN WAKSAL. "A rejection letter will include points: study size small, truly refractory, data base flawed."

Chairman TAUZIN. So that at least by the 27th you all knew not only that a rejection letter was coming, but you knew exactly what the points of rejection would be; is that correct?

Mr. HARLAN WAKSAL. What we knew is what is written here. What was relayed to us was that there are both—there are review issues, and these were the possible review issues that we were going to see in that letter; yes, sir.

Chairman TAUZIN. Where did you get that information?

Mr. HARLAN WAKSAL. I believe that was part of our conference call dialog on the 26th and possibly on the 27th.

Mr. MARKISON. Mr. Markison, was that information relayed to you in that e-mail as well, not only that the rejection letter was coming, but it was coming for the following reasons?

Mr. MARKISON. No, sir, it was not.

Chairman TAUZIN. Do we have a copy of that e-mail that you received?

Mr. MARKISON. You should have it, yes.

Chairman TAUZIN. All right. I would like to turn to the second page, Dr. Waksal. The first item says, "No press release by BMS." The second item interests me, "Brian understands that Sam and Harlan are calling FDA to try to stop RTF. Our press release should be as vague as possible. A question, do we need to do anything at all?" Is that correct? Did you and your brother begin calling FDA to try to stop the RTF at that point?

Mr. HARLAN WAKSAL. Not entirely. We were having discussions to try to decide how to move forward and what to do. I think I mentioned earlier one of the things we decided to do was to put a letter together to the FDA to try to go ahead and stop the RTF from coming. I did not call the FDA. As you mentioned, we were not able—we were asked not to contact them. I do know that Sam Waksal did try to contact the FDA.

Chairman TAUZIN. What is confusing about these documents is that in press releases you and your brother, either one of you, both of you have said that you were shocked on the 28th to find out that the RTF came down. You were shocked, utterly, to find out that the agency would reject filing. And yet these documents indicate that you knew at least on the 27th and your testimony is that Mr. Markison advised you on the 25th that the rejection letter was coming. Why would you say publicly on the 28th that you were shocked?

Mr. HARLAN WAKSAL. Well, I was shocked, sir. When I received the RTF letter, the tone, the content was a big surprise. We were surprised at the number of issues that were raised and the deficits that were noted in the RTF letter.

Chairman TAUZIN. But you had to know it was coming. You just testified you knew it was coming.

Mr. HARLAN WAKSAL. I knew that it——

Chairman TAUZIN. And you knew why it was coming.

Mr. HARLAN WAKSAL. I felt very certain that an RTF—no, these were issues—these were some of the issues, but we didn't have the extent of which were reviewed and which were going to be refusal to file issues.

Chairman TAUZIN. I want to go back if I have just a minute, Mr. Chairman, to that date when—in August of 2000.

Mr. HARLAN WAKSAL. Yes, sir.

Chairman TAUZIN. When ImClone and FDA met to discuss a possible accelerated approval strategy. Our investigators tell us that very clearly FDA relied upon the wrong version of the 9923 protocol. And then they tell us that ImClone did not correct the FDA's mistake. We further learned from the senior FDA official who overruled the medical reviewer handling the case that she believes she was misled by ImClone about its claim that a human clinical trial showed no single agent activity. We have two instances here where, one, the FDA relied upon a wrong version and our investigators tell us that no one at ImClone corrected the FDA's mistake. Did you know in August of 11, 2000 when FDA made the decision to rely upon the wrong version of the protocol that they were making a mistake?

Mr. HARLAN WAKSAL. First of all, the FDA had both versions of the protocol prior to our meeting on August 2000, and indeed we assumed, and I still believe, that the FDA was fully aware of what those protocols are. It is a surprise to me that it is suggested that we were somehow trying to fool them into thinking we were working under Version 1.0 versus Version 2.0. There would be no reason for us to——

Chairman TAUZIN. Well, clearly, they made a mistake, but our investigators said it was within your power to correct the FDA mistake in August 11, 2000. Why wouldn't you, for the sake of getting this drug approved more quickly and correctly, have corrected the FDA's mistake on that date?

Mr. HARLAN WAKSAL. We would have absolutely corrected the mistake had we known about it. The first I have heard about this issue of Version 1.0/Version 2.0, sir, is here.

Chairman TAUZIN. We were also told, however, by the FDA official who overruled the local review, that they believe they were misled by ImClone about the claim that a human clinical trial showed no single agent activity. Do you deny that?

Mr. HARLAN WAKSAL. Yes, absolutely deny that. We were very clear with the FDA that the best way to use this drug, based on the information we had in animal studies and even in the single human study that we had engaged in, did not show major single agent activity, that it is primarily a cytostatic drug. The only study that was performed in humans was the study we did in renal cell cancer, and we articulated those results, albeit in a different tumor type.

Chairman TAUZIN. I am looking at the protocols——

Mr. HARLAN WAKSAL. Yes, sir.

Chairman TAUZIN. [continuing] that are in dispute here. And staff is pointing out to me, and I am trying—I am getting this correctly, that the protocol, the original version, says that following two courses of Irinotecan, patients' tumors were measured and based on the results. Was there a change in that protocol?

Mr. HARLAN WAKSAL. Yes. Medical practice doesn't allow doctors to continue patients on a drug if they have new lesions or progression. So the doctors, in conjunction with the company, made a modification to the protocol to allow patients who were failing the drug to be on the protocol in combination with 225, or Erbitux.

Chairman TAUZIN. Well, I am looking at the minutes of the meetings with the FDA.

Mr. HARLAN WAKSAL. Yes.

Chairman TAUZIN. A meeting on August 11. And they are saying that in fact this is the original version and that it was changed later and that that is what they relied upon in literally making the decision to overrule the medical reviewer and to approve this protocol. Do you deny that?

Mr. HARLAN WAKSAL. I am not aware of any of that. I am aware of the fact that both protocols have been submitted to the FDA, and I felt that both protocols——

Chairman TAUZIN. We were told that you saw these minutes, did you not?

Mr. HARLAN WAKSAL. The minutes to——

Chairman TAUZIN. To the meeting.

Mr. HARLAN WAKSAL. Yes, I have seen the minutes to the meeting. I would like to see them again. I am not quite sure which part you are referring to.

Chairman TAUZIN. Well, we will come back to it. We will get you copies and I will ask the chairman to give me a unanimous consent to come back to it in a minute. I want you to see it as we discuss it.

Mr. HARLAN WAKSAL. I would appreciate it, Congressman Tauzin.

Mr. GREENWOOD. The Chair thanks the gentleman. The Chair recognizes the gentlelady from Colorado for 5 minutes.

Ms. DEGETTE. Thank you, Mr. Chairman. Dr. Waksal, it is your view that the problem with this Erbitux application is irregular paperwork, right, in essence?

Mr. HARLAN WAKSAL. Well, that is one of the major problems, and I think——

Ms. DEGETTE. Well, what are the other major problems?

Mr. HARLAN WAKSAL. I think it was pointed out very carefully, when you have a problem in documentation, it affects the entire study.

Ms. DEGETTE. So, in essence, it is documentation, right? Yes or no.

Mr. HARLAN WAKSAL. Yes.

Ms. DEGETTE. Okay.

Mr. HARLAN WAKSAL. But there are other issues as well.

Ms. DEGETTE. Okay. What are the other issues——

Mr. HARLAN WAKSAL. Well, the——

Ms. DEGETTE. [continuing] unrelated to documentation?

Mr. HARLAN WAKSAL. The other issues that need to be resolved are the protocol violations that took place as well.

Ms. DEGETTE. And those are serious problems too, right?

Mr. HARLAN WAKSAL. Every clinical study has protocol violations—every study.

Ms. DEGETTE. Right.

Mr. HARLAN WAKSAL. The real question is whether the protocol violations affect the integrity of the trial.

Ms. DEGETTE. Okay. Sir, I apologize, they only give me 5 minutes.

Mr. HARLAN WAKSAL. I understand.

Ms. DEGETTE. And so with respect to the documentation, now have you—you have had 6 months since you heard about this, roughly.

Mr. HARLAN WAKSAL. That is correct.

Ms. DEGETTE. Have you fixed the documentation problems?

Mr. HARLAN WAKSAL. What we have done—we can't just fix the problems, we have to fix the problems the right way.

Ms. DEGETTE. Okay. So the answer would be no.

Mr. HARLAN WAKSAL. No, that is not——

Ms. DEGETTE. In 6 months you have not.

Mr. HARLAN WAKSAL. [continuing] really the answer. The answer is what we have done is we have gone down the process and started discussions with the FDA to make sure——

Ms. DEGETTE. The answer is—Okay. I am sorry, I only have 5 minutes. The answer is you have not fixed the documentation problems. Your view is you are working on it, right?

Mr. HARLAN WAKSAL. That is right.

Ms. DEGETTE. When do you think they will be fixed?

Mr. HARLAN WAKSAL. I can't give you that answer.

Ms. DEGETTE. Okay. Now, the other problem, that is a harder problem just to fix than documentation; is that right?

Mr. HARLAN WAKSAL. Which one is that?

Ms. DEGETTE. The problem of the irregularities, the protocol violations.

Mr. HARLAN WAKSAL. No. We believe that the vast majority of these, the vast majority don't affect the ability to evaluate this study and program.

Ms. DEGETTE. So how are you working to fix that problem?

Mr. HARLAN WAKSAL. The same way. We are going through, making sure we can identify which of these violations have any impact on the ability to interpret the data and we are doing it patient-by-patient, making sure that can indeed, at the end of the day, have an intact trial.

Ms. DEGETTE. When do you expect to have all of that data to the FDA?

Mr. HARLAN WAKSAL. Well, what we are doing is that is an analysis plan.

Ms. DEGETTE. So you don't have a firm time when you expect to have that.

Mr. HARLAN WAKSAL. Until we have guidance from the FDA, we cannot give you a time on that.

Ms. DEGETTE. So it is their fault?

Mr. HARLAN WAKSAL. No, it is not.

Ms. DEGETTE. Okay.

Mr. HARLAN WAKSAL. It is something that is being done in conjunction with them.

Ms. DEGETTE. All right.

Mr. HARLAN WAKSAL. It is not something we can do alone.

Ms. DEGETTE. Okay. I mean I hope—I frankly hope Erbitux works too. There are not very many drugs for colorectal cancer.

Mr. HARLAN WAKSAL. I completely agree with you.

Ms. DEGETTE. And I understand that. But here is the thing: The reason Congress approved this Fast Track procedure is so that we could get drugs that we think that would work in very serious patients.

Mr. HARLAN WAKSAL. That is right.

Ms. DEGETTE. And if we don't have any protocols at all or if we have very bad protocols, for all we know people may be applying for laying out a hand, and I don't think that is any of our goals here.

Let me talk to you, Dr. Smaldone, for a minute. Now, you say that the reason to have Erbitux approved is to get these patients who know they are dying more time, more time with their families, more time to get their affairs in order, right?

Ms. SMALDONE. That is correct.

Ms. DEGETTE. But are you aware that neither the 9923 or the 0141, the smaller trial, have measured life extension but rather they have measured tumor shrinkage?

Ms. SMALDONE. I am very well aware of that.

Ms. DEGETTE. So in fact we don't know whether or not life extension is one of the benefits of this drug at this point, do we?

Ms. SMALDONE. That is absolutely correct. That is——

Ms. DEGETTE. Thank you. Now, I was really touched by the patient that you talked about, and this is all about the patients, Michael Ann Mullinix. I am glad that her cancer seems to be gone. But I think we should be clear, as far as we know, she is the only patient who has had this result from this drug. Wouldn't that be fair to say?

Ms. SMALDONE. That is not the way I would put it.

Ms. DEGETTE. You know other patients who have had this same result?

Ms. SMALDONE. I would like to go back to our own analysis of—a reanalysis of 9923 that we conducted during the due diligence, which was done with yet another independent review group outside radiologists evaluating the scans. And——

Ms. DEGETTE. And they say that other patients have been cured aside from this one patient?

Ms. SMALDONE. There are other patients who have responded. And at the worst case of that particular——

Ms. DEGETTE. But none of them have had the cancer go away. They have had the tumor shrink, right?

Ms. SMALDONE. We cannot comment on cure at this point in time; it is way too early. These are response rates, which——

Ms. DEGETTE. And that is even true with Michael Ann Mullinix, isn't it?

Ms. SMALDONE. At this point in time, that is true, it is a response.

Ms. DEGETTE. Thank you. Okay. I have a couple of other questions. Now——

Mr. GREENWOOD. The Chair will be lenient with the time.

Ms. DEGETTE. Oh, I am sorry.

Mr. GREENWOOD. The Chair also would note that we are going to two rounds with this panel.

Ms. DEGETTE. Thank you. Thank you, Mr. Chairman.

Mr. GREENWOOD. The Chair recognizes the gentleman from Kentucky, Mr. Fletcher, for 5 minutes.

Mr. FLETCHER. Thank you, Mr. Chairman. Let me first ask Dr. Waksal some questions. You started when the initial protocol or the initial treatment protocols were enacted at some of the cancer centers, you mentioned Sloan-Kettering as one, a very well-respected cancer center, started reporting back that the results seemed very positive. Is that—how is that documented? Is that just kind of what we used to call hallway discussions, when you are on rounds and things are going very well?

Mr. HARLAN WAKSAL. Very much so. We were getting case reports—we were getting information back that was written, data was starting to come in, a lot of it was discussions with the doctors at these various institutions around the country. There were about 20-some different centers who were using the drug in this trial. A

lot of it I think you could characterize it as hallway type of, anecdotal type of discussions, sir.

Mr. FLETCHER. Do you have documentation of that from reputable oncologists that participate in these protocols that from their experience say that, yes, in fact this drug seems to be effective, people who have had experience in a number of protocols and wouldn't say that without adequate experience?

Mr. HARLAN WAKSAL. I think every one of the physicians who were involved in our trial, every one of them, are very reputable, and——

Mr. FLETCHER. Do you have documentation, written documentation, memos, et cetera, coming from those in the early parts of these trials?

Mr. HARLAN WAKSAL. We have better than that. We have their case report forms. We actually have the documentation of the effects it was having in their patients, the fact that they were seeing shrinkage. And that is documentation that forms the basis for what we did.

Mr. FLETCHER. So these are early reports that are made throughout the protocol of the effectiveness.

Mr. HARLAN WAKSAL. Exactly. That is right.

Mr. FLETCHER. Let me go on. There appears substantial failures, or Dr. Weiss mentioned 20-some percent of those that were enrolled should have been ineligible, at least that was the number that I recall him giving. Now, apparently, you acknowledged there was some failure in following the eligibility criteria. Is that correct or not?

Mr. HARLAN WAKSAL. Yes, I do, sir.

Mr. FLETCHER. And you have said that that happens or at least problems happen in all or most protocols.

Mr. HARLAN WAKSAL. Yes. And if I could elaborate, I will give an example. The major protocol deviation that took place was for patients who had an abnormal liver test that was done, and doctors will also use their judgment to decide if an abnormal liver test put the patient at any increased risk. The doctors would go ahead and put patients on this trial in spite of that, and in fact it was their decision that it wasn't a risk to these individuals.

Mr. FLETCHER. So these very well-respected clinicians would enter someone in the trial that was not eligible because of elevated liver function test which was part of the protocol. I mean they had to have normal liver function tests, I assume.

Mr. HARLAN WAKSAL. Yes.

Mr. FLETCHER. Do you think that was because of the optimism that they saw in the response in patients that were looking for some sort of treatment? Why would that occur if they knew that it may possibly prevent this from being approved through the FDA?

Mr. HARLAN WAKSAL. I don't think that was part of their consideration. It was their clinical judgment that these patients were not being put at any type of risk by enrolling them in the study, and——

Mr. FLETCHER. But aren't they under sort of obligation to follow the protocol? Isn't it not approved for those patients to be on this under the FDA guidelines of this protocol if they do not meet the criteria?

Mr. HARLAN WAKSAL. There is no question. These doctors don't have the protocol in their hands as they go ahead and make the decisions at times.

Mr. FLETCHER. Is that normal that physicians are not fully familiar with the protocol when they are using it?

Mr. HARLAN WAKSAL. They are familiar with the protocol, but, as I said, mistakes happen in every study regardless of what that study is.

Mr. FLETCHER. I am just trying to get to the basis of why there seemed to be an excessive amount of failure in meeting the protocol in this study compared to other studies. Any answer to that?

Mr. HARLAN WAKSAL. I can. I think that the most important issue with this trial is that it was never initiated as a registration study, it was a Phase II study.

Mr. FLETCHER. Well, the Phase II, but also the Fast Track aspect, do you think that influenced it?

Mr. HARLAN WAKSAL. No. It actually—it wasn't planned for Fast Track until after we had the data. It was really the fact that we had such robust responses in patients that led us to go ahead and move this drug forward. So it was the positive data that indeed stimulated our desire to move this forward.

Mr. FLETCHER. Thank you, Dr. Waksal. Let me ask Dr. Smaldone a question. Given the fact that your company obviously being one of the leading providers for oncology therapies has been through the FDA process multiple times, you have a tremendous—much greater experience than ImClone has, in your experience, in looking over what happened here, do you think this is an FDA failure or is it a failure on ImClone's part to not follow the protocol and not adequately communicate with FDA what they are doing?

Ms. SMALDONE. I can't answer that directly, but I would like to provide you my perspective that hopefully can give you——

Mr. FLETCHER. If you can do that briefly, we would appreciate it.

Ms. SMALDONE. I will try to give you some perspective here. I think as we came into this picture, what we saw before us was a product that had a substantial pre-clinical profile that was very exciting, very strong potential for what it may be able to do in terms of inhibiting this particular receptor. There was data that was conducted by reputable oncologists, already presented to ASCO, which is a premier Scientific Congress for Oncology, that validated our understanding of the data. ImClone Systems was in very advanced discussions with the FDA, was already in Fast Track, already with a rolling BLA submission process underway, and the BLA responsibilities, the responsibility of ImClone.

And as we went through all of this, as well as very extensive due diligence, from our perspective, what we saw was a promising antitumor agent, there were issues, in fact issues that you have before you that were raised that were both scientific and regulatory issues. But from our perspective, in conversations with ImClone, it seemed that these were issues that were under discussion with the FDA and that people seemed to be at least aware of them.

Mr. FLETCHER. So let me say, given this perspective—and my time has expired, so let me just finish with this—is this an FDA Fast Track procedural problem or is this an ImClone problem?

Ms. SMALDONE. I believe that what we saw was an FDA Fast Track that appeared to, in a sense, that was a validator that the protocol and the data that was coming forward was appropriate, because we didn't have any reason to believe otherwise. We were not in direct contact with the FDA. Everything was happening through ImClone Systems.

Mr. FLETCHER. A company doesn't invest that much money without probably substantial oversight with the experience you have. Back to it, FDA problem, ImClone or both? What do you think?

Ms. SMALDONE. I really can't comment specifically.

Mr. FLETCHER. Okay. Thank you. My time has expired.

Mr. GREENWOOD. The Chair thanks the gentleman. The Chair recognizes the gentleman from Florida for 5 minutes. And before doing so would inform the committee that after Mr. Stearns' inquiry we will then recess for the series of votes until 2:30.

Mr. STEARNS. Thank you, Mr. Chairman. Dr. Waksal, you had indicated when the chairman was talking to you that if the information was not public, you didn't think it was material. I think that is what you said or did you not, sir?

Mr. HARLAN WAKSAL. No, I did not say that. I said that——

Mr. STEARNS. Do you remember what you said?

Mr. HARLAN WAKSAL. Yes. We didn't have material or public information at the time. There was not material information to disclose to the public, sir.

Mr. STEARNS. Okay. And so when Dr. Lee, at least we understand that Dr. Lee heard from the FDA about the possibility of this refusal-to-file letter. You are saying you did not know from her whether this was fact or not or she told you and you knew?

Mr. HARLAN WAKSAL. The conversation is similar to someone driving down the street and coming to a stop light.

Mr. STEARNS. Okay.

Mr. HARLAN WAKSAL. Red, yellow or green.

Mr. STEARNS. Right.

Mr. HARLAN WAKSAL. And it was not a conjecture of what——

Mr. STEARNS. No, I understand. But you had the impression that there could be a refusal-to-file letter from the FDA after talking to Dr. Lee on December 4; is that possible?

Mr. HARLAN WAKSAL. No, I did not.

Mr. STEARNS. Okay. Did you have any inkling at all?

Mr. HARLAN WAKSAL. No, I did not have any inkling until after December 12, sir.

Mr. STEARNS. Okay. Dr. Smaldone, you have indicated that this drug has great possibilities, and you have indicated a women has taken it and has been successful. That was your testimony.

Ms. SMALDONE. Thus far, yes.

Mr. STEARNS. Thus far.

Ms. SMALDONE. Yes.

Mr. STEARNS. So your company, the impression of you and the executives of Bristol-Myers is that this drug someday will be available and will be effective; is that true?

Ms. SMALDONE. That is correct. The assessment of our company was, and continues to be to this day, that this drug has promise and has activity as an anti-tumor agent. And in fact we have a

number of dedicated personnel, probably over 50 people, that continue to work on it across the company.

Mr. STEARNS. I understand. Did you see the "60 Minutes" CBS story about it?

Ms. SMALDONE. I did not.

Mr. STEARNS. Did you read the Business Week story about it?

Ms. SMALDONE. I did not.

Mr. STEARNS. Okay. Mr. Markison, did you see the "60 Minutes" story?

Mr. MARKISON. No, sir; I did not.

Mr. STEARNS. Okay. And Dr. Waksal, did you see the "60 Minutes" story?

Mr. HARLAN WAKSAL. Yes. It was a story we did not participate in, sir.

Mr. STEARNS. Did you think it was hyped or was it accurate?

Mr. HARLAN WAKSAL. The story was about compassionate use of the drug, and it highlighted two families, one that received it and one that did not.

Mr. STEARNS. Well, the claims that the story indicated by inference, did you think they were exaggerated or were they accurate?

Mr. HARLAN WAKSAL. You would have to remind me about specifics. I looked at the story as a very negative one for the company, sir.

Mr. STEARNS. You did.

Mr. HARLAN WAKSAL. Yes, sir.

Mr. STEARNS. Okay. In 1999 and the year 2000, during ImClone's annual shareholders meeting, they were asked to approve the right for yourself and your brother Sam to acquire millions of stock options to exercise at certain prices to acquire ImClone common stock in the future; is that correct?

Mr. HARLAN WAKSAL. That is correct.

Mr. STEARNS. And why was that done?

Mr. HARLAN WAKSAL. We had been building the company, invested—well, I can speak for myself, I have invested 18 years of my life in building this company from the ground up, and I believe the stock options are reflective of the effort and the time and the hard work that I have done over this course of time.

Mr. STEARNS. And how much total did you have in stock options at that point, approximately, just approximately?

Mr. HARLAN WAKSAL. I can tell you where I ended up at the end of the day, just so you know.

Mr. STEARNS. Okay.

Mr. HARLAN WAKSAL. In terms of stock option, 2 million shares as of 2001, and warrants of 500,000.

Mr. STEARNS. Okay. And at the height of the market, so they would be worth, what, $100 million?

Mr. HARLAN WAKSAL. They would be worth at the height of the market? That didn't include my shares as well. I had a total of 3.6 million shares.

Mr. STEARNS. Okay.

Mr. HARLAN WAKSAL. So at the height of the market, $210 million.

Mr. STEARNS. $210 million.

Mr. HARLAN WAKSAL. That is correct.

Mr. STEARNS. Okay. On December 6, it shows you disposed of 700,000 shares, valued at roughly $75 for $50 million.

Mr. HARLAN WAKSAL. That is partly correct. I didn't dispose of them. I did not sell shares. What I did I entered into a pre-pay which allowed me voting rights on those shares and the upside potential of those shares, and it was part of a plan that I had had for months and months to go ahead and not only diversify but pay the taxes I owed on stock options that I had gone ahead and purchased as well as a result of the Bristol transaction.

Mr. STEARNS. Did you execute the trade so that you actually received $50 million?

Mr. HARLAN WAKSAL. Actually, $44 million.

Mr. STEARNS. $44 million. Okay. Did the company loan you money to do this?

Mr. HARLAN WAKSAL. No, it did not.

Mr. STEARNS. Okay. So you just based it then on a transaction put or call so that you wouldn't have to have a loan then or you had the money?

Mr. HARLAN WAKSAL. No. That was—I believe you are mixing up a couple transactions.

Mr. STEARNS. I probably am.

Mr. HARLAN WAKSAL. Yes. And if I could help with this, I wouldn't mind, sir.

Mr. STEARNS. Oh, sure. You can help me with this.

Mr. HARLAN WAKSAL. In July—well, in January of 2001, I purchased my warrants, 500,000 shares. Again, a strong vote of confidence on my part about the company and where it was going. In July of 2001, I purchased a little bit over two million shares. It was trading at around $42 a share, and I am sure you are aware that when you purchase stock options, you need to pay taxes on that.

Mr. STEARNS. Oh, yes.

Mr. HARLAN WAKSAL. And it was for those shares that I received a loan from the company at prime interest plus 1 percent. Subsequently, I also engaged in the Bristol-Myers tender offer that took place and sold stock into that, and that paid for the loan I had taken from the company, the stock I had—the taxes on the stock I had purchased, the stock options. And, subsequently, I had another tax that I needed to pay on the monies that I had gained from Bristol Myers, since I didn't have any cash other than what was going to pay for the stock and go to taxes, sir.

Mr. STEARNS. Okay. I will just conclude because my time is up and we have to vote.

Mr. HARLAN WAKSAL. No problem.

Mr. STEARNS. I mean it seems to me you are intimately aware of the money that you are going on your stock options and how you are going to buy it. Yet the 9923 protocol that your company prepared and when we asked Dr. Weiss earlier about it, he said there were three serious problems with this: Patient eligibility criteria was not strictly defined, he talked about changing the dose and administration frequency, and he also said that the whole thing was such that you get so many vague answers. And we have a prominent oncologist who said that the overall protocol that was asked, that was created by your company, was not tightly written and efficient. The protocol generated far more questions than could be an-

swered. It was just a production for vague answers. Yet it seems like you understood intimately all this about your own money, but the actual protocol that your company developed seemed to be vague and prominent oncologists say that it wasn't a good criteria. And then the FDA asked you to come back because the clinical procedures, you didn't even complete the application, and you admit in your opening statement that the application had flaws to it.

So I am just a little puzzled why you seem to be so knowledgeable on everything about your warrants and about your own money, yet when it comes to actually applying to the FDA for the proper clinical procedures, you didn't get the full information in. And in developing the 9923 protocol, you missed out in terms of the criteria. Does that make sense?

Mr. HARLAN WAKSAL. Well, I think your confluence of information is——

Mr. STEARNS. Interesting interpretation.

Mr. HARLAN WAKSAL. [continuing] a little questionable. I don't really see the point that we were not paying attention. We were indeed. It happens to be that I differ on some of the opinions you have raised about——

Mr. STEARNS. You would agree you were paying attention with your own money, though.

Mr. HARLAN WAKSAL. Well, I was paying attention to the company.

Mr. STEARNS. Your warrants and all your options, yes. Thank you, Mr. Chairman.

Mr. GREENWOOD. The time of the gentleman has expired. The Chair would note that there is 1 minute and 14 seconds before this vote closes. The committee will recess until 2:30 with apologies to the witnesses.

[Brief recess.]

Mr. GREENWOOD. The Subcommittee will come to order. The Chair thanks the witnesses for their forbearance. We do not expect any more interruptions today. And the Chair recognizes the chairman of the full committee, Mr. Tauzin, for inquiry.

Chairman TAUZIN. I thank you, Mr. Chairman. I believe we have copies now, Dr. Waksal, of the documents that I was referring to. Do you have those copies?

Mr. HARLAN WAKSAL. Yes, I do.

Chairman TAUZIN. Let me make sure that you have them now, and will the staff make sure that he has them. What I would like to have you have in your possession is the copy of the minutes that you have indicated that you had reviewed, and a copy of the January 12 letter from the Department of Health and Human Services to ImClone approving the fast track designation.

Staff, would you make sure that those copies are available to the witness. While we are doing that, let me ask you a couple of questions and then we will get you those copies. Do you know whose handwriting these notes are in? Could you help me with that?

Mr. HARLAN WAKSAL. Yes, I do. They are notes taken by my chief financial officer, Dan Lunch.

Chairman TAUZIN. Okay. So all three of these pages are taken by him?

Mr. HARLAN WAKSAL. I believe so, sir.

Chairman TAUZIN. And I see a snake at the bottom of page three I take it?

Mr. HARLAN WAKSAL. Excuse me?

Chairman TAUZIN. There is a snake on the bottom of page three, I thought. I thought it would be a pretty identifiable little scribble, and it is his work; is that correct?

Mr. HARLAN WAKSAL. I don't know about his art work, sir.

Chairman TAUZIN. But it is his handwriting?

Mr. HARLAN WAKSAL. But it is his handwriting.

Chairman TAUZIN. It is his notes?

Mr. HARLAN WAKSAL. Yes.

Chairman TAUZIN. Thank you.

Mr. HARLAN WAKSAL. And by the way, for the record, happy birthday.

Chairman TAUZIN. Thank you, sir.

Mr. HARLAN WAKSAL. You are welcome.

Chairman TAUZIN. And while we are doing the handouts to you, you said that on the 26th that you began calling the team, the offices of the team, to let them know that you have received this information that a refusal to file letter was coming?

Mr. HARLAN WAKSAL. We had a working group from Bristol-Myers and ImClone, which was a routine call that we were having at the time.

Chairman TAUZIN. Right. Did you ever get to talk to your brother?

Mr. HARLAN WAKSAL. I don't remember when, but I believe on the 27th I did. I'm sure that at some point that I did, but I don't recall any specific call.

Chairman TAUZIN. Did you similarly call family members and advise them as well?

Mr. HARLAN WAKSAL. Absolutely not. I did not call any family members or friends.

Chairman TAUZIN. Can you give us any explanation why so many family members sold stock on the 27th?

Mr. HARLAN WAKSAL. I can't give any insight into that, sir.

Chairman TAUZIN. All right. Let's look at the documents now if you don't mind. The documents that I referred to are, first of all, the minutes. And if you look at page two of the minutes, which I understand are exchanged after these meetings so that both sides approve the minutes, and confirm that this is what really occurred at the meeting. Is that correct?

Mr. HARLAN WAKSAL. We do exchange minutes.

Chairman TAUZIN. Right. And if you look at page two, you will see that this is a phase two open label study following—it says following two courses of irinotecan, patients tumors are measured, et cetera. Is that correct?

Mr. HARLAN WAKSAL. I'm sorry, but I not with you quite yet. But, yes, I see it. On page three?

Chairman TAUZIN. I think page two.

Mr. HARLAN WAKSAL. Page two? One second.

Chairman TAUZIN. Page two, the middle of the page.

Mr. HARLAN WAKSAL. Yes, I see it.

Chairman TAUZIN. This defines a protocol, and this literally is the criteria of protocol; is that correct?

Mr. HARLAN WAKSAL. Well, it actually—it should. What we discussed in the August meeting in the slide presentation that was given to the FDA, and also that has been shared with this committee as well, is very clear.

It speaks to protocol, the second protocol, and the amendment that was taking place, and the enrollment criteria within that, and I shared that with committee members.

Chairman TAUZIN. But I want you to look at the letter of January 12, 2001 that we also gave you.

Mr. HARLAN WAKSAL. Yes.

Chairman TAUZIN. And in the second paragraph, it clearly refers to the fact that the fast track development program is being designated, and where refractory is defined as progressive disease during at least two cycles of standard doses of these chemotherapy drugs. Is that correct?

Mr. HARLAN WAKSAL. It says where refractory is defined as progression of disease during at least two cycles of standard doses of 5-fu irinotecan.

Chairman TAUZIN. Right. And read the next sentence for us if you don't mind.

Mr. HARLAN WAKSAL. "Please note that if the clinical development program you pursue does not continue to meet the criteria for fast track designation, the application will not be reviewed under the fast track program."

Chairman TAUZIN. Wasn't this a very clear statement from the FDA that if you deviated from the two cycle requirements of the criteria that you would not be reviewed on the fast track?

Mr. HARLAN WAKSAL. Well, it clearly shows some confusion. However, I——

Chairman TAUZIN. Well, what is confusing about that? I mean, here the FDA is saying very clearly that they are designating you on the fast track, where in fact these two cycles of standard doses apply, and this is the criteria.

And it says in the next sentence, "please note that if the clinical development program that you pursue does not continue to meet the criteria for fast track designation," that the application will not be reviewed. How confusing is that?

Mr. HARLAN WAKSAL. In March of 2000, we submitted version two, and was stamped in and received by the agency. In August of 2000, we reviewed with them specifically the only content that was specific to the protocols was version two.

And I recognize this, and I must say I didn't spend a lot of time reviewing this in this kind of detail. However, in the patients who were treated, the average number of cycles of treatment that these patients received wasn't two, but four cycles of treatment.

Chairman TAUZIN. Well, that may be an average, but the bottom line is that the FDA was clearly telling you that this is the basis upon which you are being approved. We are not going to continue you on the fast track if you deviate from it, and yet changes were made that you could have alerted the agency about, or you could have discussed with the agency.

You could have informed the agency that they were working on the wrong protocol, and you could have corrected this misconcep-

tion by the agency. And I am not being mean. I am just trying to understand.

If you really wanted to get the drug approved, and you were being told this is what we believe we are approving you on, and this is the criteria that you have got to follow under what we believe we are approving you under for fast track.

And you know that is not really what you are working on. You are working on some other iteration of it. Why didn't you inform the agency that they had approved you under a misconception?

Mr. HARLAN WAKSAL. Well, one, we always informed the agency what we were doing well before our August meeting, and during that August meeting, the only discussions presented by the company was version two. I think we were very clear throughout the time that we worked with them.

Chairman TAUZIN. But the minutes reflect something very different, and these are minutes that you reviewed and exchanged with the agency. The letter reflects something very different.

And the letter is a document we can look at, and not a conversation that was not recorded. What I am looking at in documents is very clear evidence that the agency was approving you on the fast track under the misconception that the protocol was based upon this criteria when you knew that it wasn't.

And I am not throwing and heaping blame on you. I am just wondering why if this approval process was so important to you as I know it is.

Mr. HARLAN WAKSAL. Absolutely.

Chairman TAUZIN. If it was so important to these cancer victims as you knew it was, and we know it is, why would you not at some point say to the agency that you have approved us under a misconception?

Mr. HARLAN WAKSAL. I believe I said right at the beginning when we started the questioning on this issue that at no time did I even have an understanding of the version one and version two until it was raised at this meeting. I was always under the assumption——

Chairman TAUZIN. But you did review these minutes?

Mr. HARLAN WAKSAL. Well, the company reviewed the minutes, and I am ultimately responsible for making sure that is done, yes, sir.

Chairman TAUZIN. But you are telling us that you personally did not know what I have shown you today until today?

Mr. HARLAN WAKSAL. I am telling you that, one, I didn't really look at that issue until today, but more importantly, I am still not certain that it really is an issue. That these patients were treated by their doctors using what is the standard of care.

And if a patient fails a cycle of treatment, a single cycle of treatment, with tumor enlargement or new tumors, it is unethical to continue to treat them with a second cycle of irinotecan. That's why we made the modification. It wasn't to move away from the standard of care, sir.

Chairman TAUZIN. I am not saying that you were wrong to make a modification. I am not saying that may not have been the right thing to do. But having made the modification, according to the let-

ter, you would not have been entitled to the fast track approval process. That's the point that I am making.

And yet having made the modification, and knowing that the agency was operating under this misconception, that you were going to require a criteria based upon two cycles of standard doses, you never said to them, hey, you have approved us on the basis of a wrong protocol, and I don't understand why you would not have done that.

Mr. HARLAN WAKSAL. Well, again——

Chairman TAUZIN. You did review the letter did you not, Dr. Waksal?

Mr. HARLAN WAKSAL. I have. I have reviewed the letter today.

Chairman TAUZIN. I mean, did you review it when you received it?

Mr. HARLAN WAKSAL. I clearly would have read this letter when I received it.

Chairman TAUZIN. I would have thought that you would have, too. And it very clearly says that if the development program that you have pursued does not continue to meet this criteria, which you just described in the paragraph above, the application will not be reviewed under the fast track program. I don't know how that could be any clearer.

Mr. HARLAN WAKSAL. Well, there was no deception on our part on what we were doing. We were very clear with the agency, and I believe if the agency will be given the opportunity to respond, maybe they could clarify whether or not this was a relevant issue.

I don't believe that this was a major problem as we move this forward.

Chairman TAUZIN. Well, apparently this becomes the major reason why the letter is—a refusal arrives. I mean, the agency finally recognizes that it was pursuing a course of approval here based upon a misconception.

Mr. HARLAN WAKSAL. I am not aware of that, sir.

Chairman TAUZIN. I am being corrected. I am told that they didn't realize that either until we pointed it out to them, which is really perhaps even more damning. Let me——

Mr. HARLAN WAKSAL. I don't believe that was an issue that the agency or the company focused on as being important.

Chairman TAUZIN. But that is amazing to me. It really is.

Mr. HARLAN WAKSAL. Well, I think it is because it really was not an issue that spoke to the heart of whether or not this drug was working or not. I don't believe that that is a critical component.

Chairman TAUZIN. Well, all we know is what the documents tell us, and what is concerning to us is that when an agency—our problem is looking at this process to see whether it works well, and whether it fails or not.

Mr. HARLAN WAKSAL. Yes, sir.

Chairman TAUZIN. And we are seeing a process whereby the agency approves you for this fast track, which is a special procedure, based upon a criteria clearly defined.

It gets changed, and the investigators for our committee, and in interviewing the senior FDA official, believes that in fact that they made their decisions based upon the wrong version of the protocol,

and they also state, which you have denied under oath, that ImClone mislead them about the claim of single agent activity.

So we have got a situation where we are going to have to find where the truth lies in between those two statements.

Mr. HARLAN WAKSAL. There is no question that at no time did we mislead the FDA regarding what we were doing, and again I want to emphasize that the fact that the FDA didn't emphasize this issue, even at the refusal to file time, and the fact that I didn't recognize it until today, this does not seem to be a major issue regarding why we received the refusal to file.

Chairman TAUZIN. Well, they seem to think it was a major issue when it was pointed out to them finally.

Mr. HARLAN WAKSAL. That's very possible.

Chairman TAUZIN. I want to take you to statements that your brother, Sam, made when he was chief executive officer on the 29th, as reported by Reuters. Do you have a copy of that, too?

Mr. HARLAN WAKSAL. I do not.

Chairman TAUZIN. I am going to read it to you, and we will make a copy available to you as I read it to you.

Mr. HARLAN WAKSAL. I believe I have a copy now.

Chairman TAUZIN. All right. It says that Sam Waksal, ImClone's chief executive officer, told Reuters that the agency first wants more annotation information about how the company verified that patients enrolled in these trials had indeed failed, et cetera.

It says also further down that there is a prediction that it would take only—Waksal said that company officials hope to meet with the FDA within 10 days to supply necessary information to the agency 6 to 10 weeks.

There were a lot of statements made minimizing the effect of this letter apparently of denial, and then we have something that I hope the Bristol-Myers witnesses will help me understand. We have got a confidential document. Do you have it in front of you? It is B019629.

And let me read it to you. It says, "Nancy, I agree that some, a lot, of Sam's comments are misleading, and at this point we should continue to be silent." What does that mean, and what is Bristol-Myers doing at that point?

I mean, you are hearing the chief executive officer of the company make these comments publicly, and then an e-mail is exchanged saying that we agree that some, a lot, of Sam's comments are misleading. At this point we should continue to be silent.

What is the meaning of that kind of an e-mail? Mr. Markison.

Mr. MARKISON. Well, sir, these are the comments of two people that are within the company. I am not quite sure they represent the entire company. However, we were certainly going through a period where we were trying to determine the best course of action, and that is where we were at that time.

Chairman TAUZIN. But of course the problem was that you were a partner in this operation, and you are aware that the chairman of the company is making misleading statements to the public in the middle of this crisis, or at least the comments were that you were, and that people in your company were saying that we should continue to be silent.

Mr. MARKISON. Well, sir, these again—and I am sorry to point this out, but these are just two folks within the company. And again we were struggling with the new information received, and attempting to determine for ourselves——

Chairman TAUZIN. Were these two people pretty key people in the development of this product?

Mr. MARKISON. Absolutely not, sir.

Chairman TAUZIN. They were not?

Mr. MARKISON. In the development of this compound, they had no relevant roles.

Chairman TAUZIN. No, not in the development of the compound, but in the development of or the marketing of it. They were part of the team were they not on this particular drug?

Mr. MARKISON. Both of them were part of the team.

Chairman TAUZIN. And they are saying in an e-mail that Sam is making misleading comments. But let's just be silent.

Mr. MARKISON. Sir, I can't tell you if they are talking to themselves. I am not a party to this. This is the first time that I have seen it. I am acknowledging clearly that Bristol-Meyers Squibb was trying to assess for themselves the exact extent of what needed to be done as we go forward, and that's clearly where we were.

Chairman TAUZIN. Well, Mr. Chairman, again, I think part of what I hope we will discern, and perhaps as we proceed further with the investigation, is how in fact the fast track process can be improved. I would hate for this hearing to somehow in any way cast dispersions upon what is an incredibly important process to make incredibly important drugs more quickly available to people once they have been properly tested.

But at the same time, I suspect that we have some real problems with the way that the system works, and when an exchange of letters that looks so clear to me at this point can be so confusing to the partners involved here, and the parties involved here.

And when approvals can be based upon wrong versions of protocols, and at least in the testimony of one FDA official on a misleading claim, the bottom line is, and I think you have said it, Mr. Waksal, and you apologized for it.

But we all could have done a better job with your company and the FDA in making this process work so that an important drug could have been properly processed, and perhaps available today to the American public.

And if we can straighten it out for the future, Mr. Chairman, I think we will have learned a lot from this hearing. Thank you very much.

Mr. GREENWOOD. The Chair thanks the chairman, and recognizes the gentleman, Mr. Stupak, from Michigan, for 5 minutes.

Mr. STUPAK. Thank you, Mr. Chairman. Dr. Smaldone, you indicated that you were part of the due diligence review for Bristol-Myers Squibb before they agreed to go in with ImClone, correct?

Ms. SMALDONE. Yes, I was.

Mr. STUPAK. And in fact you sent an e-mail to your colleagues, a Peter Ringrose, and a Beth Seidenberg, concerning ImClone. And it states that on a whole, and I am quoting now from the e-mail, "that on a whole this remains a very high risk opportunity." Is that correct?

Ms. SMALDONE. That is correct. That was in June.

Mr. STUPAK. Right. In June. And then you went on and you pointed out certain critical outstanding issues that you cited. One—and again I am going to quote them There were three issues that you had here. The pivotal CRC colorectal cancer issues, single agent activity.

"The trial which is ongoing will need to be shared with us. We should attend the FDA meeting with ImClone when the data is final. There is no agreement that we could find that is reassuring regarding the activity level needed for approval." Is that correct?

Ms. SMALDONE. That is correct.

Mr. STUPAK. Okay. You go on to say that the weak dose selection rationale, "they have developed APK pharmacokinetics rationale for dose selection. However, the dose is questionable for refractory patients, and the safety margin for the early stage patient, has not been determined.

"In their phase three first line study, they are evaluating the same dose used in refractory disease. This is already seen as a problem by the FDA and us." Is that correct?

Ms. SMALDONE. That is correct.

Mr. STUPAK. And safety, you indicated again, and quoting, "that the safety of the product specifically related to skin toxicity, bleeding, allergy, has not been well categorized. This reemphasizes the weaknesses of the dose selection argument." Is that correct?

Ms. SMALDONE. Yes, that is correct.

Mr. STUPAK. And then you went on to your executive, and you point out the risk of the results of the single study agent, and again let me quote you. That "the FDA has requested that the data be provided on the anti-tumor activity of C-25 as a single agent. Pre-clinical data has thus far been provided to FDA to address this issue.

"But they have persisted in their interests that clinical data be provided. No accelerated approval has ever been granted for an oncology drug for use in a combination therapy." Is that correct?

Ms. SMALDONE. This is coming from the same memo? I'm sorry.

Mr. STUPAK. This is coming from the memo, yes, and the concerns about the single agent study and 9923 study were not completely resolved before you entered in your agreement. In fact, we have a copy of it if you would like to see it.

Ms. SMALDONE. If I may, please. Thank you.

Mr. STUPAK. Sure. Can we provide that to the witness. Here, give her this one right here, Alan.

Ms. SMALDONE. Thank you very much. Yes.

Mr. STUPAK. Okay. So no accelerated approval, and that is what you are going for here before you enter into this agreement, and this is June of 2000.

No accelerated approval has ever been granted for an oncology drug for use in a combination therapy. Is that correct? And that's really what ImClone was asking to do?

Ms. SMALDONE. Right.

Mr. STUPAK. And whether we agree if it was protocol one or protocol two here you had to have, this approval fast track was based upon the combination therapy; is that correct?

Ms. SMALDONE. That is correct.

Mr. STUPAK. Even after the rejection though. So there should be no question here that we have to have a combination therapy and there is some weaknesses here.

Bristol-Myers Squibb reviewed ImClone's application again after it was rejected in January of 2002, correct?

Ms. SMALDONE. In January of 2002, this was after the refusal to file letter, went through a full assessment again, yes.

Mr. STUPAK. Correct. Were you a part of that review?

Ms. SMALDONE. Certainly my team was, yes.

Mr. STUPAK. So you are familiar with it?

Ms. SMALDONE. Yes.

Mr. STUPAK. Dr. Weiss says that BMS review, and that performed by the independent review assessment committee. That is part of your team, right?

Ms. SMALDONE. I believe that may be referring to the independent radiology review that we pulled into place in August of 2001.

Mr. STUPAK. Okay. So, yours, plus this independent review committee, agreed that only 16 of the 21 patients admitted to the 9923 study has having progressive disease show a partial response to the combination therapy. This is 13.2 percent.

Has the FDA ever approved an oncological drug with a response rate that low using only clinical end points?

Ms. SMALDONE. Yes, they have. In fact, if I may, Congressman——

Mr. STUPAK. And what drug did they use it on?

Ms. SMALDONE. For irinotecan itself——

Mr. STUPAK. But irinotecan was not used in combination. It was used as a single agent, correct?

Ms. SMALDONE. That is correct.

Mr. STUPAK. And it also increased life expectancy of the patient as we talked about with Ms. DeGette earlier, and your drug does not increase the life expectancy of a patient. It may at best shrink a tumor.

Ms. SMALDONE. At the present time under accelerated approval regulations, which is evaluating the effect on a surrogate marker, which in this case was response rate, at the same time it is necessary to evaluate the full clinical benefit if you will with long term data, which was the plan for this program in any event. If I may just make one clarification if I may.

Mr. STUPAK. Sure.

Ms. SMALDONE. In June 1901, what I was referring to were a series of issues, scientific and regulatory issues, that were bubbling forward at that point in time, which are part and parcel of what is seen throughout the due diligence process.

One point in particular, just to get the sequence here, is that because of some of those issues that were raised, and further discussion within the company, as well as with outside experts, both oncologists, regulatory experts, we did create a separate independent review panel with radiologists that were identified to look at the 9923 data specifically, and reevaluate the responders in that particular study.

So as a result of these issues and discussions on collapsing time here, Bristol-Myers Squibb took this step to reevaluate with a separate review panel of experts that particular study on those data.

Mr. STUPAK. Right. And in the review panel and all of this review, and rightfully so, Bristol-Myers Squibb did it, and it was in January of 2002 after refusal, right? That's what I am talking about, the refusal now.

Ms. SMALDONE. No, this was before. This is prior to the time of the agreement.

Mr. STUPAK. Okay. Now, we have all of this in June when you did your memo, and you agreed with me that no accelerated approval has ever been granted for an oncology drug for use in a combination therapy. And that was your statement back then, and that's true of what you said in June of 2001?

Ms. SMALDONE. Right.

Mr. STUPAK. Now, I am bringing you to January of 2002.

Ms. SMALDONE. Yes.

Mr. STUPAK. And you have gotten your RTF, and you have been rejected, and there is an internal review that you are doing; isn't that correct?

Ms. SMALDONE. Yes.

Mr. STUPAK. You are doing it with this independent committee, and Bristol-Myers Squibb, and you are saying what happened here. And your own document says that it was agreed upon by your independent assessment committee that the 9923 study has having progressive disease show a partial response to a combination therapy.

This is 13.2, because only 16 of the 121 patients responded. And that is less than the 15 percent that it was supposed to be, correct?

Ms. SMALDONE. What we did at that point in time—and this, Congressman, was in August.

Mr. STUPAK. No, no, January, 2002. You are not familiar with any of that?

Ms. SMALDONE. I'm sorry?

Mr. STUPAK. You are not familiar with the Bristol-Myers Squibb review in January of 2002?

Ms. SMALDONE. In the January-February timeframe, we went through several internal reviews within Bristol-Myers Squibb, as well as again another panel of experts that were brought in to assess all of the information.

And at that point in time, what I believe is that the reassessment that was done in August was put forth to this group.

Mr. STUPAK. Forget August. In January of 2002, here is your draft document, confidential, Bristol-Myers Squibb, you are going through to see why you were refused, right? Are you familiar with this? It is January 11, 2002.

Ms. SMALDONE. I really couldn't say specifically. There are so many documents, and I would be happy to see it and comment if I may.

Mr. STUPAK. Okay. Did you tell our staff, the Congressional staff—you have been interviewed by them, right?

Ms. SMALDONE. Yes.

Mr. STUPAK. Right. Did you tell the staff that you would never have permitted Bristol to submit an application to the FDA of the quality of the ImClone submission of their application? Did you tell

our staff that you would never allow your company to submit an application like that?

Ms. SMALDONE. The discussion was as it relates to quality and study conduct, and quality assurance. We within Bristol-Myers Squibb work at very high standards, and after the refusal to file letter, and the extent, and the depth of the issues that were raised in the refusal to file letter, it was very clear that there were some very substantive—what I would call study conduct quality assurance types of issues, that is correct.

Mr. STUPAK. So you did tell our staff that you would never let——

Ms. SMALDONE. That's correct.

Mr. STUPAK. Okay. So, Bristol sent in an application such as what ImClone did, and you said there was some substantive issues, and that's why the refusal letter, right?

Ms. SMALDONE. Yes.

Mr. STUPAK. So it is more than just documentation?

Ms. SMALDONE. In its cumulative, it certainly appeared to be more than documentation.

Mr. STUPAK. And then in the substantive issues that the FDA raised in its refusal, the FDA was fully justified in sending ImClone an RTF based on the application that they submitted in the fall; isn't that correct?

Ms. SMALDONE. When we say, Congressman, the refusal to file letter, and went through a thorough review and evaluation of it, it became apparent that in accumulative of all of the issues that were raised there, it appeared difficult for—and I can't speak for the FDA, but based on my experience, it appeared difficult for them to reconstruct the datasets and follow the chain of evidence.

Mr. STUPAK. So if they couldn't follow the chain of evidence, and if they couldn't reconstruct it, they were certainly justified then in putting out the RTF were they not in your 17 years of experience as you said?

Ms. SMALDONE. If I can make some qualifications to that, sir. I have never seen a refusal to file letter before, and I have never since.

Mr. STUPAK. Well, the refusal to file was based upon those substantive issues that you said were lacking, correct?

Ms. SMALDONE. That is correct.

Mr. STUPAK. So if the refusal is based upon substantive issues, then the FDA was correct in putting an RTF on?

Ms. SMALDONE. I believe that it had some justification based on what I was able to see.

Mr. STUPAK. Okay. On December 4, there is starting to catch wind that maybe ImClone or that ImClone might be receiving an RTF or that there application would not be approved.

Did you or anyone from Bristol-Myers Squibb call up and say, look, what do you need to make this thing work, and can we withdraw it, or can we rework it? Did anyone do anything like that that you know of?

Ms. SMALDONE. Excuse me, sir. With the FDA, or with——

Mr. STUPAK. With the FDA. Did you call the FDA and say how can we rework this. Can we withdraw. Let us do further work on this?

Ms. SMALDONE. We are not responsible at that point in time and still are not for the BLA or any of the dialog with the FDA.

Mr. STUPAK. Thank you.

Mr. GREENWOOD. The gentleman's time has expired. The Chair recognizes himself for—well, first off, to—well, without objection, the Chair would enter into the record certain documents. The first of these is three pages of handwritten notes referred to by Mr. Tauzin.

The second is a Department of Health and Human Services document, reference number BBIND5804, dated January 12, 2001.

The third is a Department of Health and Human Services memo, dated September 22, 2000. And fourth is the e-mail referred to that is addressed to Nancy.

[The information follows:]

ImClone Systems Incorporated

12/27/01

- check w/ BMS on press release
- Rejection letter will include points
  - study size small
  - truly refractory
  - DB flawed
  -
- Confirm w/ Morgan Lewis

HCEC 21143
Confidential Treatment Requested
by Imclone Systems, Inc

FOIA CONFIDENTIAL TREATMENT
REQUESTED BY IMCLONE SYSTEMS INC.

Targeted Oncology

ImClone Systems Incorporated

Brian M. noon 12/27/01

→ No press release by BMS

→ Brian understands that:
- Sam + Harlan are calling FDA to try to stop RTF.
- Our press release should be as vague as possible
? - Do we need to do anything ∂ all

→ Allan Bennett is exploring a file over Protest

ImClone Systems Incorporated

12/27
5pm mtg.

- IRAC → NYU
- John - fax standards
- Document ⇒ Public info ??
- File over Protest
- Appeal ⇒ Lilly advises to do only if RTF due to SAS.
- Q+A, Script (2), Press Release, Timeline
- FDA Mtg. Attendees
- Basis for RTF (ML)
- Letter to FDA (ML Jan. Lewis)
- Minutes of meeting Feb/Mar. that counters Jan. minutes @

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

Our Reference: BB-IND 5804

ImClone Systems, Incorporated
Attention: Nikhil Mehta, Ph.D.
Senior Director, Regulatory Affairs
Branchburg Corporate Center
22 Chubb Way
Somerville, NJ 08876

JAN 1 2 2001

Dear Dr. Mehta:

Reference is made to your **Investigational New Drug Application (IND)** for "Cetuximab [Chimeric Monoclonal Antibody (C225) to Epidermal Growth Factor Receptor] and Chemotherapy." We also refer to your submission of November 14, 2000, received on November 15, 2000, requesting designation as a Fast Track Product pursuant to Section 506 of the Food, Drug, and Cosmetic Act (the Act).

We have reviewed your request and concluded that it meets the criteria for the Fast Track designation. Therefore, we are designating as a Fast Track development program the investigation of cetuximab in combination with irinotecan for its effect on durable tumor responses (complete and partial responses) in patients with metastatic colon cancer who are refractory to standard chemotherapy (5 fluorouracil and irinotecan), where refractory is defined as progressive disease during at least two cycles of standard doses of 5-fluorouracil and irinotecan.

Please note that if the clinical development program you pursue does not continue to meet the criteria for Fast Track designation, the application will not be reviewed under the Fast Track program.

Under the FDA Modernization Act of 1997, designation as a Fast Track product for a new drug or biological product means that FDA will take such actions as are appropriate to expedite the development and review of the application for approval of such product. FDA may also evaluate for filing and commence review of portions of an application for approval of a Fast Track product under certain conditions.

For further information regarding Fast Track Drug Development Programs, please refer to the FDA document "Guidance for Industry on Fast Track Drug Development Programs: Designation, Development, and Application Review." This document is available on the Internet at http://www.fda.gov/cber/guidelines.htm or may be requested from the Office of Communications, Training, and Manufacturers Assistance, at (301) 827-1800.

We look forward to working with you to expedite the development and review of this promising proposed use of the product. If you any have questions please contact Ms. Sharon Sickafuse, Division of Application Review and Policy, at (301) 827-5101.

Sincerely yours,

Glen D. Jones, Ph.D.
Director
Division of Application Review and Policy
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: September 22, 2000

From: Sharon Sickafuse, OTRR/DARP, HFM-588

Subject: August 11, 2000, meeting with ImClone regarding the clinical development plan for cetuximab; IND 5804

To: Attendees
File

The purpose of this meeting was to discuss ImClone's development plan for cetuximab. At this time, the sponsor's main treatment areas are colorectal and head and neck cancer.

EGFR Test Kit

All clinical studies are using a test kit manufactured by DAKO and a central lab (Impath) is performing the tests. DAKO plans to submit a PMA for the test kit and ImClone will check with DAKO to see if they have met with CDRH. FDA asked the sponsor to submit the acceptable methods of tissue handling and storage (e.g., formalin fixed, paraffin embedded blocks). They were advised to obtain tissue blocks from each patient in case these samples are needed for testing at a later date.

Pharm/Tox Issues

ImClone had recently reported the death of a monkey who died by disseminated intravascular coagulation after receiving a dose that was approximately 50% of the loading dose. FDA expressed concern over adverse event reports of bleeding in patients as well. The sponsor was asked to contact Ms. Mercedes Serabian regarding additional pharm/tox studies (i.e., a tissue cross-reactivity study) that are necessary.

Safety Issues

1. **Reported Deaths**: Of the 45 deaths, does this number also include the all deaths in the control arm of the randomized trials as well? Please submit a breakdown of the deaths by study, by dose, and by treatment arm.

2. **Skin Toxicity**: That sponsor stated that Grade 1 and 2 skin toxicity is common to most patients who receive the product and manifests as an "acne-like rash" focused on sun exposed areas. The rash never covers the whole body and resolves completely without scaring. ImClone was asked to submit photographs showing the extent of the rash and the appearance of the skin during the healing process. They were also asked to provide documentation of the incidence of pain medication and increased hydration requirements because they may be related to the skin toxicity. The sponsor was also asked if it is

possible to reduce the dose to decrease the toxicity. ImClone replied that the dose selected is one at which all the receptors are saturated. They are collecting pk data and perhaps the dose can be modified. The FDA indicated there should be mutual willingness to continue thought on this issue.

3. **Anaphylaxis**: ImClone stated that two patients so far had a reaction to the test dose, one had a reaction after the infusion, and one during the infusion. The reactions manifest rapidly and are treated with epinephrine. Reactions have never occurred on day 2. Patients are premedicated with benadryl before cetuximab is given and the infusion is administered slowly over approximately 40 minutes. ImClone stated about 50% of the patients with Grade 3 anaphylactic reactions continue to receive cetuximab and tolerate it. The other 50% are not retreated because the physician decided to stop due to skin toxicity or another reason such as progressive disease. The FDA advised the sponsor that continuedtreatment of patients with a Grade 3 allergic reaction is not recommended. Please submit a report on the Grade 3 and 4 allergic adverse events including patient narratives and intervention events, pre-medications administered and the result of rechallenge.

4. **HACA Assay**: ImClone stated that they are working on a HACA assay with the University of Alabama. The assay has been validated and they will submit information regarding the assay and its validation.

Trial Design Issues:

Protocol CP02-9923:

This is a Phase 2 open label study of cetuximab plus irinotecan in metastatic or recurrent colorectal cancer refractory to irinotecan. Following two courses of irinotecan, patients' tumors are measured and based on the results, divided into the Stable Disease Treatment Group (tumor volume change< 25%) or the Progressive Disease Treatment Group (tumor > increased in volume 25%). Patients then receive irinotecan plus cetuximab until treatment failure.

1. FDA expressed concern that because the study is a single arm trial, the effect of cetuximab plus irinotecan verus continued therapy with irinotecan alone will be unknown. To meet the standards for accelerated approval, the sponsor would have to demonstrate documentation of irinotecan failure. How many patients would fit into a more stricter definition of refractory as having progressed with in a short defined period of time starting from the beginning of therapy? ImClone replied that most of the patients would fit within this definition and that they will provide data on this. They will be documenting irinotecan failure. Patient CT scans will be digitized and the REC will review the images

2. ImClone verified that the dose(s) of irinotecan will be recorded for all patients. FDA wants to be sure that patients receive adequate doses of irinotecan and that if for some reason a lower dose is given, the reason (e.g., toxicity) is documented.

3. FDA asked whether or not it is general practice to discontinue irinotecan after two cycles if the patient doesn't respond? The sponsor clarified that as long as a patient has stable disease and acceptable toxicity, irinotecan is continued.

4. The FDA stated that the basic trial design is probably acceptable, but that we are not sure how the data on the stable disease patients can be used. FDA noted that there are similarities in the regulatory issues facing cetuximab compared to irinotecan which was approved by CDER. CBER will discuss the irinotecan approval decision process with CDER to determine what criteria were used for the definition of "failure of prior chemotherapy" and what studies were conducted and submitted in support of that application and approval. FDA strives to apply approval criteria uniformly, if possible.

5. ImClone presented a proposal of the Phase 4 confirmatory study. The patients in this study would all be newly diagnosed, EGFR positive, and randomized to either irinotecan plus 5FU/leucovorin plus cetuximab or irinotecan plus 5FU/leucovorin. The primary endpoint would be overall survival and secondary endpoints would be response rate and time to progression. The FDA agreed that this proposal was acceptable.

Protocol CP02-9816:

This is a Phase 2 open label study of cetuximab plus cisplatin for treatment of head and neck cancer that is refractory to cisplatin containing regimens. The design is similar to protocol CP02-9923. Following two courses of cisplatin, patients' tumors are measured and based on the results, divided into the Stable Disease Treatment Group or the Progressive Disease Treatment Group. Both groups receive cetuximab plus cisplatin.

1.The FDA advised the sponsor that the same concerns that were expressed regarding protocol CP02-9923 also apply here.

2.While it is acceptable to study the stable disease patients, we are unclear how you will determine if cetuximab has any treatment benefit.

3.The FDA agreed that a 15% response rate to cetuximab and cisplatin in patients that are cisplatin-refractory is clinically meaningful if the patient population is defined as those who have progressive disease. However, we recommend that the sample size be increased to a total of 75 patients with progressive disease.

Product Issues

1. FDA inquired as to the status of the comparability program. ImClone stated that they will submit the final study reports on the comparability program. Dr. Fuchs stated that she wants to see actual data, not just a summary of the means and standard deviations. A comparability protocol with proactively set specifications should also be submitted for the manufacturing site in New Hampshire.

2. FDA inquired as to the status of the viral clearance validation study. ImClone stated that this study is in process and that they will submit the final report when its done. Again, Dr. Fuchs needs to see the actual data, not just summaries.

3. The sponsor was asked to submit, in the BLA, a table delineating which lot from which manufacturing process went to each patient.

4. The sponsor was advised that the FDA considers one vial thaw to equal one lot.

Action Item for FDA:
Contact CDER to discuss regulatory process for handling of comparable regulatory questions and issues for irinotecan.

Action Items for ImClone:

1. Contact Ms. Mercedes Serabian regarding what additional pharm/tox studies (i.e., a tissue cross-reactivity study) are necessary.
2. Submit information on sample handling for DAKO EGFR assay.
3. Submit information on HACA assay.
4. Submit a breakdown of the deaths by study, by dose, and by treatment arm.
5. Submit a report on the bleeding adverse events and Grade 3 and 4 hypersensitivity/allergic adverse events including patient narratives and intervention and for the allergic events, pre-medications administered and the result of rechallenge. It would be helpful if this information was submitted electronically in addition to the paper.
6. Submit photographs of the skin toxicity and the need for palliation of the skin toxicity.
7. Submit the REC charter and composition. The FDA recommended that the REC be composed of at least three individuals: an oncologist, a radiologist, and the third person can be either an oncologist or radiologist. Schedule a telecon with Drs. George Mills and Susan Jerian to discuss design, regulatory, and administative issues related to this committee.
8. Submit revised analytic plans for studies CP02-9923 (colorectal) and CP02-9816 (head/neck) that clarifies the primary analyses for the intended patient populations.
9. Submit protocol abstracts of the confirmatory Phase 4 studies in colorectal and head/neck cancers.
10. Submit final reports (including data) on the comparability program and submit a comparability protocol with proactively set specifications for the manufacturing site in New Hampshire.
11. Submit final report (including data)on the viral clearance validation study.
12. Contact Ms. Patty Delaney regarding FDA advice/input on their compassionate use program. ImClone said that their drug supply for the clinical trials is fine, however, they can't handle hundreds of compassionate use requests. Ms. Delanay stated that she can help them develop a plan to handle these requests.

Attendees
Center for Biologics Evaluation and Research

Office of the Commissioner
Office of Special Health Issues
JoAnn Minor
Patty Delaney

Office of Therapeutics Research and Review
Division of Application Review and Policy
Sharon Sickafuse, M.S.

Division of Biostatistics
Clara Chu, Ph.D.
Ghanshyam Gupta, Ph.D.

Division of Clinical Trial Design and Analysis
Susan Jerian, M.D.
Patricia Keegan, M.D.
Richard Steffen, M.D.

Division of Communication and Consumer Affairs
Melissa Greenwald, M.D.
Julie Zawisza

Division of Monoclonal Antibodies
Chana Fuchs, Ph.D.

ImClone Systems, Incorporated
Deborah Lynch, Director, Regulatory Affairs
Michael Needle, M.D., Medical Affairs Officer
Michael Trapani, Vice President, Regulatory Affairs and Quality Assurance
Harlan Waksal, M.d., Executive Vice President and Chief Operating Officer

Merck KgaA
Tilo Netzer, Head of Group Regulatory Affairs

Consultants to ImClone
Richard Chiacchierini, Ph.D. Senior Vice President, Statistics, C.L. McIntosh
Roger Cohen, M.D., Associate Professor of Medicine, University of VA
Wan Ki Hong, M.D., Chairman, M.D. Anderson Cancer Center
James O'Brien, M.D., Medical Monitor, PharmaNet, Inc.
Leonard Saltz, M.D., Memorial Sloan-Kettering Cancer Center

9-12-00; finalized 9-22-00

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Nancy Goldfarb nancy.goldfarb@bms.com
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Nancy,

I agree that some alot of Sam's comments are misleading and at this point we should continue to be silent. As you heard from yesterday's discussion, there's alot we don't know.

A

Nancy Goldfarb wrote:

> Adriann,
>
> Once we see the statement ImClone plans to use in conversations with
> reporters and investors, we should determine what our key message points
> will be, for both internal and external audiences.
> At this point, it's clear we'll need to go beyond our original comment,
> and decide what we want to say about the issues raised by the FDA in its
> letter, and timing matters.
>
> Take a look at Sam Waksal's comments in the Reuters story, below, where
> he gives details and dates.
>
> We can discuss all of this next week, perhaps even in person, rather
> than during another 8:00 a.m. conference call!
>
> Nancy
> ---
> UPDATE 3-ImClone says FDA refuses cancer-drug application
>
> (adds details, CEO and analyst quotes, paragraphs 1, 3-4, 6-8,
> 10, 14-15, 17-19)
> By Ransdell Pierson
> NEW YORK, Dec 29 (Reuters) - ImClone Systems Inc <IMCL.O>

> said on Friday it expects the launch of its experimental colon
> cancer treatment, Erbitux, to be delayed until at least the
> third quarter of 2002 following questions by U.S. regulators
> over the drug's clinical data.
> Earlier in the evening, ImClone said regulators had refused
> to accept its application to sell Erbitux -- a setback for the
> potential blockbuster which was to be co-marketed by
> Bristol-Myers Squibb Co <BMY.N> to patients who had failed
> previous chemotherapy treatments.
> Sam Waksal, ImClone's chief executive officer, told Reuters
> the agency first wants more "annotation" information, about how
> the company verified that patients enrolled in its trials had
> indeed failed previous drug regimens and that subsequent tumor
> reductions attributed to Erbitux were indeed real.
> Concerns raised by the FDA mainly involve how the data were
> presented and do not raise outright concerns about the safety
> or efficacy of the drug, the CEO added.
> ImClone filed its marketing application in late October for
> Erbitux. The drug had already been granted "fast-track" status
> by the FDA, meaning it was to be reviewed within six months
> rather than the agency's standard 12-month period for
> determining the fate of new medicines.
> Waksal said company officials hope to meet with the FDA
> within 10 days and to provide the necessary information to the
> agency in six to 10 weeks.
> But the task of gathering the material will delay the
> planned May, 2002 launch of Erbitux until at least the summer
> of that year, he said.
> "I think we can have the drug on the market in 2002,"
> Waksal said, a timetable that some industry analysts said is
> likely but far from certain given the FDA's trend in the past
> two years of giving special scrutiny to novel medicines.
> HIGH HOPES, HIGH PROFILE
> Erbitux has been considered one of the most promising new
> experimental treatments for cancer because of its apparent
> ability to knock out cancer cells without harming healthy
> tissue.
> In one of the biggest biotech partnerships in history,
> Bristol-Myers earlier this year agreed to buy $1 billion of
> ImClone's stock and pledged up to another $1 billion in
> periodic payments to the tiny company for the right to
> co-market Erbitux.
> In return, Bristol-Myers received rights to keep about 40
> percent of profits from Erbitux, a product which many analysts
> have predicted could rack up annual sales of at least $1
> billion.
> "So far, this is not looking like a very good deal for
> Bristol-Myers," said Hemant Shah, an independent drug analyst
> who predicted Erbitux will eventually be cleared by the FDA.
> The injectable medicine, a monoclonal antibody, is designed
> to block a protein called epidermal growth factor receptor
> (EGFR) that is found on the surfaces of many types of cancer
> cells.
> Shah said Erbitux and other experimental anti-cancer drugs

> that block the same protein are extremely promising, but that
> their very novelty may prompt the FDA to be doubly careful to
> assure their safety and effectiveness.
> "There are potential long-term issues with regard to side
> effects of these drugs," said Shah, who noted that
> Anglo-Swedish drugmaker AstraZeneca Plc <AZN.L> sought FDA
> approval on Friday for an EGFR blocker called Iressa meant to
> treat lung cancer.
> BIOTECH CAUTIONARY TALE
> Shah said shares of ImClone could fall sharply on Monday
> because of the almost certain delay for its lead drug, but that
> Bristol-Myers' selloff will be tempered by the fact it already
> sells an array of highly profitable medicines.
> "This is another good example of the risky nature of
> biotech products, 90 percent of which fail to survive," said
> Shah.
> Matt Geller, a drug analyst for CIBC World Markets,
> speculated ImClone will not have to conduct additional clinical
> trials of Erbitux to satisfy FDA concerns.
> "The good news is that the FDA is not challenging the
> safety or efficacy of the drug or the design of the drug
> trials. They're challenging the form in which the data were
> submitted," Geller said.
> Bristol-Myers spokeswoman Nancy Goldfarb said she was
> unable to provide an additional comment.
> ImClone shares fell $3.05 to $55.25, or 5 percent, on
> Friday on the Nasdaq. They have traded in the past 52 weeks in
> a range between $23.37 and $75.45.
> Shares of Bristol-Myers slipped $1.05, or 2 percent, to
> $51.80 on the New York Stock Exchange.
> ((Health Desk, 646 223-6034))
> REUTERS
> Rtr 00:37 12-29-01
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Mr. GREENWOOD. The Chair recognizes himself for 5 minutes for inquiry. Dr. Markison, I would like to go back to the way that you learned of the refusal to file letter. How did you learn that was going to happen?

Mr. MARKISON. Well, sir, there was a series of events throughout the month of December, an inkling it seems on December 4, and as the month progressed, certainly there was——

Mr. GREENWOOD. It is an inkling that Dr. Lee described as three equal possibilities?

Mr. MARKISON. That's the way that Dr. Lee described it.

Mr. GREENWOOD. But you had an inkling that there was a greater likelihood of the three possibilities?

Mr. MARKISON. There was an inkling, sir, and quite frankly that was in essence the beginning in my mind anyway of——

Mr. GREENWOOD. It was an inkling in your mind?

Mr. MARKISON. It was an inkling in my mind, yes.

Mr. GREENWOOD. And how did that inkling get into your mind?

Mr. MARKISON. That it was mentioned as a possibility.

Mr. GREENWOOD. Mentioned by whom?

Mr. MARKISON. Dr. Lee reported it from the FDA dialog.

Mr. GREENWOOD. But did she say that it was more likely that there would be a refusal to file letter than that there would be an approval?

Mr. MARKISON. No, sir.

Mr. GREENWOOD. She just mentioned it as one of two or three equal possibilities?

Mr. MARKISON. Dr. Lee just reported to our group on the results of her conversation.

Mr. GREENWOOD. Okay. All right. And then on December 20th, there was a teleconference, which we referred to earlier where it was apparent that the FDA had made or come to a decision and told ImClone not to call them, and that they would receive their decision on the 28th.

At that point, we had been working with Alan Bennett, outside counsel, for some time off and on, and he was familiar with the project, and I asked him if he could find out any more information that would be helpful, because at this point it was not definitive.

Mr. Bennett then responded to me on Christmas Eve, as I have stated, in writing, and was——

Mr. GREENWOOD. What time of day was that on Christmas Eve?

Mr. MARKISON. I believe it was in the early evening because I was trying to head out the door with my children for Christmas mass.

Mr. GREENWOOD. Okay. So you were in the office when you received that?

Mr. MARKISON. No, I was at home, sir.

Mr. GREENWOOD. You were at home when you received that information from Mr. Bennett early in the evening?

Mr. MARKISON. Yes.

Mr. GREENWOOD. And then who was the next person—who was the first person with whom you shared that information?

Mr. MARKISON. Well, I left the house, and came home, and tried to reach Harlan Waksal, and again failed, and did not leave a message on his machine. I called him the next day and also——

Mr. GREENWOOD. So you didn't share this information with anyone else over Christmas Eve?

Mr. MARKISON. On Christmas Eve, no, sir. But on the next day, Christmas Day, it was shared within my company certainly.

Mr. GREENWOOD. Well, Mr. Bennett knows the information, and Mr. Bennett gives the information to you. Does Mr. Bennett give the information to anyone else?

Mr. MARKISON. He was also corresponding with Mr. Keene, legal counsel to Bristol-Myers Squibb, and Mr. Costa, also legal counsel to Bristol-Myers Squibb.

Mr. GREENWOOD. So Mr. Bennett informed those two gentleman on Christmas Eve, as well as he informed you?

Mr. MARKISON. They received a copy of the same e-mail that I did.

Mr. GREENWOOD. A copy of the same e-mail. Okay. So the first person that you shared this information with was whom?

Mr. MARKISON. I believe it would have been Harlan Waksal, or additionally I spoke to Cheryl Anderson, who is in regulatory affairs in our company as well.

Mr. GREENWOOD. This is on Christmas Day?

Mr. MARKISON. On Christmas Day, yes, sir. And I wanted to make sure that Cheryl communicated with the appropriate——

Mr. GREENWOOD. Did you share the information with anyone else at ImClone?

Mr. MARKISON. I only spoke to Dr. Waksal on this Christmas Day.

Mr. GREENWOOD. And did you call anyone else at Bristol?

Mr. MARKISON. Yes, sir, I did. I called Cheryl Anderson. I believe I also called my supervisor at the time, Mr. McBlaine, to inform him, and I believe I may have spoken to other people in the company at that time, but quite frankly I can't remember all of them.

Mr. GREENWOOD. Did you inform those folks at Bristol before or after you spoke to Harlan Waksal?

Mr. MARKISON. I can't recall exactly, sir, because I know that I made a number of attempts to call Dr. Waksal, and I did not want to leave this message on his machine.

Mr. GREENWOOD. Mr. Waksal, I have a copy of a letter signed by your brother, Sam Waksal, and sent to the ImClone Board of Directors, on July 18, 2001. It appears that the purpose of the letter is to inform the Board that you and your brother had borrowed over $30 million from the company to exercise over 4 million options. Is that true? Have you seen that letter?

Mr. HARLAN WAKSAL. Can I see a copy of that letter, please?

Mr. GREENWOOD. While Mr. Waksal is looking at that, Mr. Markison, do you know how Sam Waksal did find out? You couldn't reach him, but do you know how Sam Waksal found out about the refusal to file letter?

Mr. MARKISON. No, sir, I do not.

Mr. GREENWOOD. You have no idea?

Mr. MARKISON. No.

Mr. GREENWOOD. Harlan Waksal, Dr. Waksal, do you have any idea how your brother learned of the refusal to file letter?

Mr. HARLAN WAKSAL. As I mentioned, I had told the senior management team about the refusal to file letter, or the potential for

the—the strong potential for a refusal to file letter, and I believe he spoke to the head of investor relations at the company, Andrea Rabney, when he arrived sometime in the evening of the 26th.

Mr. GREENWOOD. Have you had a chance to glance at that letter?

Mr. HARLAN WAKSAL. I'm sorry, I was. Just 1 second. But I am familiar with it. It was asking for permission to get a letter, a promissory note from the company to go and exercise the stock.

Mr. GREENWOOD. So did you and your brother borrow the $35 million to exercise the 4 million shares on July 12, knowing that you would use these shares during the tender offer from Bristol?

Mr. HARLAN WAKSAL. No. We did exercise our options, and we did enter into a promissory note with the company at the time that the Bristol deal was not completed, and due diligence was still ongoing.

And, in fact, at the time we already had strong discussions with outside counsel that we could go ahead and do conditional exercise of the stock options. But I certainly would not have had to purchase the options, but could have used the stock options themselves in the offer if indeed we went down that pathway.

So they were different types of issues. I exercised the stock because of the price of $42 a share, and my feeling that the company was going to continue to do strong, and continue to move forward, and in flexion points would add value to this, and that I wanted to gain the long term value of that equity in the company, and that is why I have so many shares today. I still believe that.

Mr. GREENWOOD. Did you know by the end of June that Bristol-Myers Squibb was going to purchase roughly 20 percent of the company?

Mr. HARLAN WAKSAL. At the end of June, we had various discussions with Bristol, and options included them purchasing more, but 20 percent was around the number that we were negotiating at that time.

Mr. GREENWOOD. How likely did you think that by the end of June that that was to happen?

Mr. HARLAN WAKSAL. In truth, I had been down this pathway so many times with companies that I felt at that time that it had probably a 50-50 chance of taking place.

Mr. GREENWOOD. And did that have anything with the decision of you and your brother to exercise those options at that time?

Mr. HARLAN WAKSAL. I can't speak for Sam. But it had no impact on my exercising. If it had to do with a tender offer, and the question is economically what would have made more sense, it would have been simply to tender my stock options rather than exercise them, which would still have resulted in whatever financial gain.

What I did was buy a stake in ImClone. It was a promissory note that was paid back. No money was given to me. I bought a large stake in my company, which I still hold today. I still have two million shares of ImClone stock, sir.

Mr. GREENWOOD. My time has expired. The Chair recognizes the gentleman from Kentucky, Mr. Fletcher.

Mr. FLETCHER. Thank you, Mr. Chairman. I wanted to ask just a few questions following up.

Mr. GREENWOOD. Excuse me, but the gentlelady is being very polite in allowing Dr. Fletcher to go ahead.

Mr. HARLAN WAKSAL. I hope this level of politeness continues in this direction as well.

Mr. FLETCHER. Dr. Smaldone, when we asked Dr. Waksal about compliance with the protocol, it mentioned that—and let me preface this by saying is this going through the refusal to file letter here, there seems like—and maybe it is just in retrospect, but I think you probably share that.

But there is a lot of discrepancies here that are rather obvious. If you can document CT scans on results with irinotecan before you begin the combined therapy, you have no base line, and there was some problems there.

But one of the things that was stated is that—for example, it mentioned the elevated liver function test and some other things of folks who have may been entered into the study that were not eligible, was that the oncologist may not have had the specific protocol right there in front of him.

And my recollection, and we have had patients entered into protocols, and we have worked with protocols personally, and generally there is a whole team that works. Often times nurses that screen these patients, and they are very thorough, and the protocol is very clear.

It is outlined in fact to assure that you meet the FDA criteria. All of these things are checked off and file forms are written, and all the criteria is written down. So how does that happen that these were entered and maybe some oncologist didn't know that they met the protocol? That seems odd to me.

Ms. SMALDONE. It seems odd to me, too, sir. I really can't comment beyond that.

Mr. FLETCHER. I mean, these are not fly by night oncologists. These are probably the world's experts. Oncologists is what we are talking about. I mean, is the protocol that poorly structured, and was it that poorly organized.

I know that there are mistakes and things like that that we make, and we are humans, and there are times where there are deviations, or because of clinical reasons that you have to depart from the protocol.

But these are things that are clearly aberrations, and I just wondered from your standpoint if you have ever seen anywhere where protocols are done where the clinician doesn't have the protocol in front of him.

Ms. SMALDONE. Normally, that is not the case, sir.

Mr. FLETCHER. Okay. Dr. Waksal, if you could maybe respond to that. I know that you said, well, maybe they didn't have it in front of them. I assume you are a clinician as well.

Mr. HARLAN WAKSAL. I am, but I can't give an explanation on it. It was not because of a lack of clarity in the protocol. Why it took place, I don't know. I can tell you that the majority of these had to do with what I mentioned before, the liver function test problems.

And in fact that is something that makes the patient sicker. It means that these patients were a little bit more else. So the doctors must have felt, and I am speculating, must have felt that they still

were going to be given a drug that would not result in an adverse event.

But I am really speculating. I don't know why it took place.

Mr. FLETCHER. Well, I just find that very concerning, because most of the oncologists that we have worked with, as well as other clinicians in different areas, have done FDA studies, phase two.

Mr. HARLAN WAKSAL. This study was done at the University of Colorado, at Memorial-Sloan-Kettering, at the University of Alabama, at UCLA. It was done at prestigious institutions across the country, and with clinicians that were very good at doing these types of trials.

Mr. FLETCHER. Let me ask Dr. Smaldone. Are those normally done with a lot of intervention, or at least oversight from a company that is sponsoring these, to go in and make sure that there is compliance all along the protocol, and was that a problem with ImClone?

Ms. SMALDONE. I can tell you what we do, Congressman, which is there is significant oversight on the part of our clinical teams, our clinical monitors, or indeed the contract research organization if the study is contracted out to a research organization to assist in the clinical monitoring and study conduct.

That's what we do, and I can't say exactly what the——

Mr. FLETCHER. To ensure things like some of these patients where they simply did not have any adequate CAT scans, which are pretty obvious that those kind of mistakes are not made.

But let me ask you—and I want to ask both of you. Dr. Smaldone, from your standpoint, how much communication took place in your review, and I assume that you have reviewed this, especially since the refusal to file letter.

How much communication took place on these concerns prior to the refusal to file, because I think Dr. Waksal, you said that on December 28, or even a few days before, that you were quite surprised at the refusal to file.

Mr. HARLAN WAKSAL. Yes.

Mr. FLETCHER. So obviously in your mind there was not the adequate information from the FDA that the data that you were giving them was not adequate or that the protocol was not stringent enough as they said it wasn't conducted properly.

Mr. HARLAN WAKSAL. Actually, my comment was that I thought it was reparable, and I knew that there were issues, but I thought that they were all issues that we could go ahead and fix.

Mr. FLETCHER. Okay. Dr. Smaldone.

Ms. SMALDONE. Sir, we did not review the clinical program of ImClone. So we——

Mr. FLETCHER. But did you review all the communications and everything that answered between—Dr. Lee, I assume that you were seeing the clinical aspects of that. Did you review all the communications to see where in the world—I mean, it is bound to have caught you by surprise as well.

Ms. SMALDONE. Congressman, we did a very extensive due-diligence review of the scientific aspects, pre-clinical aspects, and clinical, regulatory, financial, full-team of people reviewing this.

There are however certain levels of expectations on the part of the proposed partner that the study conduct, ways of approaching

good clinical practice, and quality assurance, would be conducted as would be conducted with any pharmaceutical company according to guidelines.

So it was with total hindsight at this point that some of those expectations were not met, but we did not review the program, and we were certainly not there to participate in any of the specific dialogs between ImClone as a sponsor in any of their clinical investigators.

Mr. FLETCHER. Okay. Thank you. Well, it is just that in my experience that clinicians rarely deviate from a protocol that is pretty well understood, especially if it is done well.

Let me just say that the thing that really concerns me here is that you have got obviously the financial ramifications, the investors, and some of the other things. It is very, very important.

And not only that, but it is just as important, and probably even more so, is the expectations, and it appears that the financial influence of this, particularly from the executives of ImClone, drove raising patient expectations, and that is very concerning.

And I just wondered, Dr. Waksal, in retrospect, what would you have done differently to have prevented this debacle and tragedy actually?

Mr. HARLAN WAKSAL. Well, it is a tragedy, and I think most importantly one point that seems to be left out, and we talk about certain documentation, and one point that is left out is the response rates in these patients, and the response rates, which is really critical.

And it wasn't survival, but other drugs have been indeed approved based on response rates, including irinotecan. Survival data came later that these types of effects that we are seeing in patients were remarkable, and we tried to give some testimonials.

In fact, there is a patient here today, Amy Cohen, who again has been treated with this drug, and who had benefit, and I think that the most important thing that we did wrong—we are a small company, and we didn't have the resources to do some of the quality checks that needed to be done.

We worked with outside groups, and clinical research organizations to do that work with us and for us. Unfortunately that is where the errors took place, in the quality and making sure that quality was intact. And we are working now continuously to reconstruct this to the best of our ability.

Mr. FLETCHER. Thank you. Mr. Chairman, one thing I would just recommend. If we have clinical trials that are FDA approved, and they are being conducted, and clinicians are not—in other words, if a company requires to have the kind of oversight to ensure that clinicians are not following the protocol, I think we have got some significant problems here. And I just wanted to add that to my closing. Thank you.

Mr. GREENWOOD. The Chair thanks the gentleman and recognizes the gentlelady from Colorado, Ms. DeGette, for 5 minutes.

Ms. DEGETTE. Dr. Waksal, you said that you have provided testimonials from patients who have been helped by this drug. Would that include the letters that we have received in this committee?

Mr. HARLAN WAKSAL. That's correct.

Ms. DEGETTE. And if I understand it, all of the letters that we have received in this committee have been received because the patients are getting the drug under the compassionate-use doctrine, which does not require pre-approval by the FDA; is that correct?

Mr. HARLAN WAKSAL. I believe that is correct. I am not sure, but I believe that could be correct.

Ms. DEGETTE. And, Dr. Smaldone, is that your understanding as well, that these patients who have been helped, have been helped under the compassionate-use doctrine, and that in fact for these colorectal cancer patients who have no other help, that your company and ImClone can provide the drug to them without pre-approval by the FDA. Would that be correct?

Ms. SMALDONE. I am not aware of what testimonials were sent to the committee. I am very sorry. So I really can't comment.

Ms. DEGETTE. Okay. But as far as you know, Erbitux could be provided to colorectal cancer patients without any other alternative under the compassionate-use doctrine.

Ms. SMALDONE. Under compassionate-use, it can, yes.

Ms. DEGETTE. Thank you. Now, I just have a couple of more questions, Mr. Chairman. I do apologize, but I am going to have to leave to go get on an airplane because of the forest fires in my State, and so I will try to be quick because I want to hear a lot of what the FDA says.

As I understand it, Mr. Markison, and also Dr. Smaldone, your company invested $2 billion in ImClone, right, Mr. Markison?

Mr. MARKISON. Well, we invested $1 billion for nearly 20 percent of the company, and then we paid—we structured a transaction that would have us paying another billion dollars for the right to market the product.

Ms. DEGETTE. So that answer would be yes, $2 billion?

Mr. MARKISON. We have not paid the $2 billion.

Ms. DEGETTE. You have paid only $1 billion?

Mr. MARKISON. $1 billion, plus $200 million up front.

Ms. DEGETTE. Thanks. So I would think as a business man that you would want to make sure that there was some efficacy to a drug before you invested $1 billion plus, correct?

Mr. MARKISON. That's correct, ma'am.

Ms. DEGETTE. And, Dr. Smaldone, as I understand it, the due diligence review that was done before this business decision was made was that the patient who had a positive response were the only ones that were looked at, is that correct?

Ms. SMALDONE. The patients that had a positive response to Erbitux were reevaluated by an outside expert group that we brought in as part of the due diligence, that is correct.

Ms. DEGETTE. And what else was done as part of the due diligence?

Ms. SMALDONE. We went through extensive evaluation of this product that identified many of the issues that we had talked about, and also evaluated this product and the entire arrangement, including the manufacturing capacity, and there were other things that were looked at as part of this.

Ms. DEGETTE. But in terms of the efficacy of the drug, what else was done aside from this independent review of the 27 patients that had a positive result?

Ms. SMALDONE. This was discussed internally and externally, and we went to outside experts. It was discussed with many individuals, including individuals that have since come to the company who had been experts in the field at the National Cancer Institute in the U.S.

Ms. DEGETTE. So you didn't recreate any of the critical trials?

Ms. SMALDONE. We could not recreate any of the critical trials. Those were not possible to do.

Ms. DEGETTE. Those were done in 1999, right?

Ms. SMALDONE. That was accepted as work done by ImClone, correct.

Ms. DEGETTE. Okay. So when you had your independent experts review, the 27 patients with the positive response, the results went down from 22 percent to 13 percent, correct?

Ms. SMALDONE. That is correct.

Ms. DEGETTE. And yet based on that, with 27 patients out of a roughly 130 some patients study, 27 patients with a positive response, in your independent review, it went down by 11 percent; from 22 percent to 13 percent.

But yet your team felt that was worth a $2 billion commitment for financing?

Ms. SMALDONE. After everything was said and done, and all the assessments were made in this review, which was essentially doing everything against the drug, and this was the worst case scenario analysis that was done, we believe that this drug had positive potential, and that at the end of the day was an agent that had promise for cancer.

And again if you consider a 13 percent response rate with an unmet medical need in a setting where patients have no other alternative, and if this were a family member of anyone of the committees, I would think that this would be seen as something very important.

Ms. DEGETTE. Now, wait a minute. First of all, Dr. Smaldone, if there was no other alternative, they could get the drug under compassionate use, right? I mean, the question that we are asking today is should the FDA approve this drug as a drug to be used by all patients in colorectal cancer, which would mean that you would want to have some kind of—I mean, that's why we do trials, is to make sure that the drugs work.

And not just on one patient, but at a high level of percentage, and what I am asking you is a pretty simple question. You felt that 13 percent was adequate.

Ms. SMALDONE. Not only did we feel, but this was reviewed with many experts, and that was thought to be an important response rate in this particular setting of metastatic colorectal cancer, where really a response rate at this point in time of something of that magnitude is really unheard of.

Ms. DEGETTE. Mr. Chairman, excuse me, but I am out of time. I just want to say, Mr. Chairman, that I think something else for us to look at here is how a company could be so dead sure of the efficacy of a drug to put a commitment of $2 billion in, and then only a few months later come back in January and say, oh, we reexamined the data, and we found it very, very defective. That is a mystery to me.

Mr. GREENWOOD. The Chair recognizes Mr. Stearns of Florida for 5 minutes.

Mr. STEARNS. Thank you, Mr. Chairman. There was a 1993 article in Barrons, and it talked about some of the loans that you folks made, and it said that ImClone loaned Sam Waksal $70,000 and gave him a miscellaneous cash advance of almost $90,000.

And the loans in advance were repaid with interest, but the following year another loan of $117,000 non-interest bearing cash advance was made to him again. And then in the end, 9 months ending December 31, 1992, the company loaned him another $275,000.

These loans of course were on top of his salary and bonuses, and made him one of the best paid biotech CEOs. Now, according to Barrons, because of failed business ventures, Waksal needed the money to renovate his apartment, where he featured a collection of modern art and ancient relics.

And when Barrons raised the question of the issue of borrowing, your chairman, Robert Goldhammer, disclosed a new no loan policy. He said the money is paid back, and would not be loaned to him again. So it is a historical event, rather than an ongoing one. But according to the SEC's filings, your company continues to make personal loans, and no interest cash advances to Sam Waksal over the last several years. So the question is are you continuing to make loans, and did Mr. Goldhammer not tell the truth about his no loan policy, or did you change it again, and what is the policy today?

Mr. HARLAN WAKSAL. Well, I can speak about the policy today, and I think it is critical for you to know that the company has appropriate governance in place that loans to officers will not be made.

There are certain circumstances that will allow monies to be—promissory notes to be given. For example, stock option types of exercises, which is part of the stock option plan, as long as one can support the ability to pay it back.

Mr. STEARNS. Well, Barrons is talking about the personal loans, and it was said back in 1992 that we will not do this any more the chairman said, and so now you are saying that it is a policy now of no personal loans; is that what you are saying today?

Mr. HARLAN WAKSAL. As the president of the company, I am telling you that there will not be further loans to officers of this company.

Mr. STEARNS. Okay. But you understand that they were done in the past, even after Mr. Goldhammer said that we won't do it any more. Isn't that true?

Mr. HARLAN WAKSAL. I don't know the context of the interview, but I do know that loans were given after that comment was made.

Mr. STEARNS. Okay. At the time that you and your brother granted millions of more options in 1999, weren't you and your brother trying to sell the company?

Mr. HARLAN WAKSAL. Many times during the course of this company, in 1998, 1999, 2000, we met with a variety of companies, and entertained possibilities of ventures, including mergers and acquisitions.

Mr. STEARNS. Okay. At the time that ImClone accelerated the vesting of these options so that they would vest if the stock price

climbed, wasn't ImClone trying to sell a majority equity interest in publicizing its attempt to get FDA approval?

Mr. HARLAN WAKSAL. Well, no, sir. Actually, the stock options that were granted, the stock option itself was one that was triggered by increases in stock prices. The incentive was based on an increase in stock price.

The company at the time was having discussions, and it wasn't as if we were——

Mr. STEARNS. Did you change the policy? I don't think in the original policy it was set up that way?

Mr. HARLAN WAKSAL. Not to my knowledge.

Mr. STEARNS. Okay. At the time that you and other ImClone insiders got millions of dollars in loans from ImClone in mid-July, weren't you deep in negotiations over the tender offer with Bristol, and it was clear that the premium price for shares tendered would be $70 when it was trading at $50?

Mr. HARLAN WAKSAL. We had a discussion on this earlier, and indeed, as I pointed out, my exercise of the stock at that time was based on my belief and faith in the company.

I was able to tender into that offer with a conditional—with just using my stock options. I didn't need to exercise those stocks. In fact, one that did was it raised money for the company because the monies weren't borrowed. Although I had a promissory note, they were repaid to the company.

And what it did was increase my position in the company, which I still hold today, quite considerably.

Mr. STEARNS. Were other shareholders aware, and did they have the opportunity to get loans?

Mr. HARLAN WAKSAL. Shareholders, or people with stock option plans?

Mr. STEARNS. Either one.

Mr. HARLAN WAKSAL. It is a part of the stock option plan, yes. It is a standard part of our stock option plan.

Mr. STEARNS. But the shareholders could not get these loans that you and your brother could get?

Mr. HARLAN WAKSAL. Well, shareholders don't have stock options, sir. These are stock options.

Mr. STEARNS. But the point is that you were able to get these loans and the shareholders were not, right?

Mr. HARLAN WAKSAL. It was a promissory note. We didn't get cash from the company. We owed the company money, and it was an exercise of those options. And, yes, that is not something that the shareholders can do unless they would have stock options in the company.

Mr. STEARNS. Now, when you get these promissory notes, did you sign them personally?

Mr. HARLAN WAKSAL. Yes, I did.

Mr. STEARNS. And what did you put up for collateral?

Mr. HARLAN WAKSAL. What I had to represent to the company was my stock, and the stock——

Mr. STEARNS. You put up stock for collateral?

Mr. HARLAN WAKSAL. There was no stock transfer to the company, but I demonstrated to the company where the stock was, and that it was unencumbered.

Mr. STEARNS. Because if I go to the bank, I have to put up either collateral or I have to sign personally?

Mr. HARLAN WAKSAL. I signed personally and I needed to show to outside counsel, as well as counsel of the company, my ability to use my stock to repay that loan.

Mr. STEARNS. So the collateral was the stock?

Mr. HARLAN WAKSAL. Yes, it was.

Mr. STEARNS. On a promise that it would go to X, Y, Z?

Mr. HARLAN WAKSAL. No, sir, it was on no promise of anything. This was a non-recourse promissory note. They could ask for it back and it had nothing to do with stock price. In fact, if I had chosen at the time to go out and to sell my stock, at where it was trading at $42 a share, I could have done so.

Mr. STEARNS. And this is the last question, Mr. Chairman, and I will let you go. Is the advantage of a tender offer that it allows the largest shareholders to sell massive amounts of stock in 1 day without the disruption caused by day to day selling to work off a block of shares?

Mr. HARLAN WAKSAL. No, I don't believe that at all. I think the benefit of a tender offer is to make sure that all shareholders can equally participate if they choose to in an opportunity to divest whatever percentage of shares that would be.

Mr. GREENWOOD. The Chair thanks the gentleman. We are just about to dismiss you, and I have one quick line of questioning for Mr. Waksal, and I would have preferred to ask these questions of your brother were he willing to testify.

Do you have the same secretary that he had when you took over as CEO? Do you have the same secretary as your brother had on at least the 27th of December?

Mr. HARLAN WAKSAL. I have a different administrative assistant. However, the administrative assistants are now part of a corporate office that I have established to administer to the other senior people in the company.

Mr. GREENWOOD. I think you have in front of you a phone log from December 27, and of course the committee has been interested, as the SEC has, and others, in who knew what that might have been inside information.

And this shows—and I am just looking at some of the names and some of the messages that might have had something to do with the selling of shares. Carl Icon called at 11:05. A Mr. Weissbroad—do you know who Mr. Weissbroad is?

Mr. HARLAN WAKSAL. Yes, I do.

Mr. GREENWOOD. Who is he, sir?

Mr. HARLAN WAKSAL. I believe he is a fund manager.

Mr. GREENWOOD. Okay. He called regarding shares. Bob Cicuchi; do you know who he is, sir?

Mr. HARLAN WAKSAL. I do not.

Mr. GREENWOOD. Okay. Martha Stewart. Something is going on with ImClone, and she wants to know what. She is on her way to Mexico, and staying at Las Ventanas. Jarrett, and I assume that is Jarrett Posner, a son-in-law of Sam, called.

Mr. HARLAN WAKSAL. That's correct.

Mr. GREENWOOD. Do you know from discussions with the person who made this phone log, or by any other means, whether Sam

conveyed information back to any of these folks about the status of the company with regard to their refusal to file a letter?

Mr. HARLAN WAKSAL. I have no information regarding that.

Mr. GREENWOOD. Okay. And you have not learned from an administrative assistant or secretary, and whether any of these calls were returned?

Mr. HARLAN WAKSAL. I have not. The only information that I have heard is what has been really in the press, and otherwise, I am not familiar with any calls being returned or the kind of calls.

Mr. GREENWOOD. Was your brother, Sam, in the office that day?

Mr. HARLAN WAKSAL. I believe so, but I would have to tell you that I was in Colorado at that time, and so I can't tell you absolutely.

Mr. GREENWOOD. Well, did you speak with your brother on that day?

Mr. HARLAN WAKSAL. I did.

Mr. GREENWOOD. And where was he when you spoke to him, or where did you reach him?

Mr. HARLAN WAKSAL. I don't remember. I just don't remember if I called him or me. It could have very well been at the office, or on his cell phone. I just don't recall.

Mr. GREENWOOD. Okay. And you were in contact with other company officials that day in the office. You called the office and talked to other folks at ImClone?

Mr. HARLAN WAKSAL. We had a conference call that morning and certainly we were in discussions during that time, yes, sir.

Mr. GREENWOOD. But you have no way of knowing whether any of these phone calls were returned by Sam or by anyone else?

Mr. HARLAN WAKSAL. I would have no way of knowing that.

Mr. GREENWOOD. I thank you, Mr. Waksal, and I thank you, Dr. Lee, and thank you, Mr. Markison, and thank you, Dr. Smaldone.

Mr. STEARNS. Mr. Chairman, I think there has been some requests to put some documents in the record. Just so the record is clear, I had asked about the BMS memo of January 11, 2002.

We have a copy here, and I would ask that this copy in its entirety be placed in the record.

Mr. GREENWOOD. Without objection, the document will be placed in the record.

[The information referred to follows:]

DRAFT DOCUMENT

OF

PRELIMINARY FINDINGS

FROM THE REVIEW OF THE BLA

ERBITUX

Cetuximab
BMS CA225

Study IMCL CP02-9923
Phase II Study Of Anti-Epidermal Growth Factor Receptor (EGFr) Antibody Cetuximab In Combination With Chemotherapy In Patients With Advanced Colorectal Carcinoma

and

Study IMCL CP02-0141
Phase II Study of an Anti-Epidermal Growth Factor Receptor (EGFR) Antibody, Cetuximab, in Patients with Irinotecan-Refractory, Stage IV Colorectal Carcinoma

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Prepared by:
Erbitux Clinical Team

Date: January 11, 2002

BMS CONFIDENTIAL MATERIAL

EXECUTIVE SUMMARY

1.0 The Plan

2.0 Review of BLA

2.1 IMCL CP02-9923

2.2 IMCL CP02-0141

2.3 Plan to Collect Additional Data

2.4 BMS Review of Erbitux BLA Clinical Pharmacology Data

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1.0 PLAN

The following is developed based on review of the RTF letter from the FDA and is circulated for input. Essentially, the BLA was refused on three grounds:

- **Scientific**: Failure to isolate the contribution of irinotecan and failure to establish the dose and schedule of administration of Erbitux.
- **Methodologic**: In the opinion of FDA Study 9923 is not adequate and well controlled. Specifically, the study population is not well characterized, there are a number of deviations from the protocol in eligibility, treatment plan and other study conduct parameters.
- **Presentation and Organization**: Numerous discrepancies and omissions from the efficacy dataset and the safety dataset make it impossible to review.

1.1 BACKGROUND MATERIALS

1. 21CFR 601.2(a)
2. CBER Refusal to File Guidance
3. Guidance for Industry: Providing Regulatory Submissions to CBER . . .
4. ImClone Systems Inc. FDA minutes: August 11, 2000
5. FDA letter to ImClone Systems Inc.: January 19, 2001
6. FDA telephone contact: January 26, 2001
7. FDA letter: March 27, 2001

1.2 OBJECTIVES

Design and implement a process to resubmit the BLA for Erbitux:

Evaluate Study 9923 and assess if it can be clearly qualified as adequate and well controlled.

If so, implement the process for updating the data with additional prior therapy information and regenerating datasets and prepare a Final Study Report from the study in a manner which will be readily analyzed by FDA

Evaluate Study 0141 in an identical manner with the objective of re-analyzing and resubmitting these data alongside Study 9923

Review and update other studies included in the BLA with the objective of including in re-submission of new BLA with update of the ISS and ISE. Highest priority given to Emerck comparative protocol of C225 vs. C225 plus CPT-11 and Head and Neck data.

Develop evidence in support of dose and schedule of C225 and prepare integrated dataset as specified by FDA.

Develop additional pre-clinical evidence for combination use of C225 with irinotecan.

Discuss and develop additional new protocols for rapid execution in support of a new BLA.

1.3 ADEQUATE AND WELL CONTROLLED

1.3.1 Protocol Violations

BMS to conduct a review of the CRFs and/or data base to identify all patients who violate one or more eligibility criteria (Study 9923 and Study 0141)

BMS to conduct a review of the CRFs and/or data base and identify all patients who had an irinotecan dose change or schedule change coming on study (Study 9923 only).

Identify all patients whose had dose adjustments or dose delays of C225 while on study and determine if these were according to protocol (Study 9923 and Study 0141).

Identify all patients who had dose adjustments or dose delays of irinotecan while on study and determine why these occurred. Since the protocol did not specify specific dose modification parameters for irinotecan, document reasons for dose adjustment may need to be developed (Study 9923 only).

Identify all patients whose dosing with C225 was continued in the face of toxicity which, according to protocol, should have resulted in discontinuation (hypersensitivity, severe skin rash, etc.; Study 9923 and Study 0141).

Identify all patients who violated on study procedures for response determination (missing scans, inappropriate timing of scans, lack of confirmation of response; Study 9923 and Study 0141)

1.3.2 Establishing Refractoriness (Both Study 9923 and Study 0141)

For each patient obtain the start and stop date of prior irinotecan treatment and the best response to prior irinotecan treatment. Also obtain the date of best response and the date of progression on irinotecan.

Per the FDA letter there is no information on individual or summated tumor measurements **prior to and after irinotecan treatment.** Therefore, we should try to obtain more scans for each patient, their BASELINE scan prior to irinotecan, a second scan corresponding to the time of best response to irinotecan and/or a scan documenting progression on irinotecan and use these as comparators against the baseline scan obtained at entry to Study 9923. Some of these scans might already be in the BLA, however, the best way to try to confirm this is by understanding as completely as possible the relationship of the scans to the dates identified above. Update the database with this additional data.

Retain an independent radiologist to provide tumor measurements from all comparator scans and on-study scans to assign patients to PD or SD cohorts.

For those patients who had a treatment free interval prior to starting on Study 9923 or Study 0141, obtain documentation of the reasons for this 'drug holiday' and develop patient narratives for the study reports. Include supportive analysis of efficacy which excludes these patients.

1.3.3 Efficacy

Ask an independent radiologist to read on study scans to determine response based on standard criteria as above, and the tumor measurements to be entered into the database.

Write an analysis plan for Study 9923 and Study 0141 with consistent efficacy definitions for Study 9923 and Study 0141. In this plan should be one definition of complete response, one definition of partial response and one definition of progressive disease based on accepted criteria (WHO, RECIST or an agreed modification based on consultation with the FDA).

> *The issue of overlapping confidence intervals is most relevant if the identical response criteria are applied across studies. This is not the case in the current BLA and needs to be corrected in a re-submission.*

Using the analysis plan, conduct an internal assessment of response based on the tumor measurements in the CRFs and enter the response in the database.

> *In the interest of time and efficiency my opinion is that we should not re-convene the IRAC. Moreover, in reading the FDA letter, I see no compelling reason for us*

to do so. The most efficient thing for us to do is to provide a completely new efficacy database for the study.

1.3.4 Safety

Provide patient narratives for all deaths, dropouts and serious and unexpected adverse events in Study 9923 and Study 0141. Determine if other studies in the BLA are lacking required narratives and provide those as well.

Provide a safety database for Study 9923 and Study 0141 which is clean and consistent from the CRF to the database. Discuss whether this will require BMS to re-enter all CRF data into a new database or if the existing Pharmanet and BBI database can be appropriately cleaned and re-submitted.

1.4 PRESENTATION AND ORGANIZATION

Simply put, discrepancies and omissions must be eliminated in any re-submission for a refractory colorectal cancer claim.

We need to discuss the merits of BMS re-entering all CRF data into a new database or trying to update the existing PharmaNet, and BBI, and if required, QI2 datasets attempting to eliminate discrepancies and omissions.

If we elect to 'start from scratch' with the radiographic review of the patients, the QI2 dataset becomes irrelevant. It is replaced by a new BMS dataset. Frankly, this might be preferable, as my impression is that the radiology efficacy dataset is more complicated than it needs to be.

1.5 SCIENTIFIC GROUNDS

1.5.1 Failure To Isolate The Contribution Of Irinotecan In The Combination

In order to construct sound, scientifically based arguments in support of the efficacy in Study 9923 and Study 0141 we need to first have an idea of the results using identical response criteria as discussed above. We then may need to develop further comprehensive arguments as to why overlapping confidence intervals from studies with small sample sizes are not necessarily indicative of a lack of contribution of irinotecan.

Assess the status of the Emerck protocol and review the document in detail for consistency with our revised analytic plan for Study 9923 and Study 0141. We may need to discuss face to face with Emerck a joint analysis plan across all three studies.

Plan additional pre-clinical experiments with irinotecan and C-225 in irinotecan resistant animal models to see if the existing pre-clinical data can be independently verified.

1.5.2 Failure To Establish The Dose And Schedule

Assess the likelihood of the existing PK data to support the dose and schedule recommendation. Review carefully the PK/PD data which was supplied in the BLA and assess the robustness of any relationships between PK and tumor burden, tumor EGFR expression etc. as stated in the letter.

Review carefully the DAKO submission in parallel with this activity. If the DAKO test is unreliable from the very start, then our ability to use existing EGFR expression data to explore for PK-EGFR relationships is severely compromised without new data.

Develop and implement the necessary ClinPharm studies required to fully answer the FDA's list of deficiencies. Assuming we can convince FDA that Study 9923 and Study 0141 are suitable for review, these ClinPharm issues may become of secondary importance and might be explored as post-approval commitments.

1.6 OTHER ITEMS

1.6.1 Head and Neck Protocols

Identify studies that will allow an indication in SCC HN. Review these protocols and CRFs for inconsistencies similar to those in the colorectal protocols.

Write analyses plans and integrated plans for evaluating efficacy via an independent radiologist.

Discuss the need for entering these data into BMS database and assuming responsibility for all analytic work.

1.6.2 New Studies

We obviously will need to design new protocols, however, prior to finalizing these, we need to have some idea of the true response rate based on a re-analysis of Study 9923 and Study 0141. New protocols will need to be discussed with the FDA.

We need to finalize and implement the first line study.

1.6.3 New BLA

Given the scope of the deficiencies cited in the FDA letter, we need to plan for a major writing effort in the re-submission of a new clinical data package to the BLA. This would likely include re-generating all the major documents in the clinical portion of the submission including study reports for Study 9923, Study 0141, the ISS and the ISE.

2.0 REVIEW OF BLA

2.1 IMCL CP02-9923

2.1.1 IMCL CP02-9923 PROTOCOL VIOLATIONS

2.1.1.1 Eligibility

A total of 37 patients had at least one inclusion/exclusion criteria that did not qualify them to be eligible for the study. Of the 37 patients, 25 patients were ineligible due to hematology or chemistry values that were outside the range required by the protocol (15 of the 25 patients were given exemptions to be enrolled in the study). Among the group of patients who were ineligible for reasons other than hematology or chemistry abnormalities, two patients (patient numbers 035728 and 066632) responded to Erbitux therapy (see Table 1).

TABLE 1 ELIGIBILITY BY INCLUSION/EXCLUSION CRITERIA[1]

	No. of Patients Ineligible[2]
Inclusion Criteria	N=139
1. Confirmed CRC	0
2. SD/PD definitions	2[3] 035728, 020649 066703
3. EGFr expression	0 066714, 066726
4. Bidimensional/Non RXT disease	1[4] 020635
5. PS≥60 ≤	1
6. ICF	4[5]
7. ≥ 18 years	0
8. Adequate hematologic function	1 039641, 075723
9. Adequate hepatic function	24
10. Adequate renal function	0
11. No prior chemo/RXT tox	0
12. No prior cancer (3 years)	2[6]
13. Effective contraception	*can not be assessed* 4 pts to D/C prog that D/D pt(+)
Exclusion Criteria	
1. Prior MAB therapy	1 066632, 066714
2. Surgery within one month	1
3. RXT within two months	1
4. Chemo after irinotecan	2
5. Significant cardiac disease	0
6. Significant neuro disease	0
7. Pregnant/breast feeding	1 (not pregnant)
8. No investigational agent (one month)	0

1. Eligibility criteria from version 2.0 of protocol dated 18OCT99. One patient (patient number 035601) was entered under version 1.0 of protocol and was eligible per protocol criteria except for alkaline phosphatase and is included in the above table.
2. A total of eight patients had more than one reason for ineligibility (patient numbers 035607, 060602, 063609, 060667, 066689, 066719, 060721, 502699).

3. Patient 035728 (SD) irinotecan dosing 17APR00 - 19JUN00; patient 066703 (SD) 12APR00 - 03MAY00
4. One patient (patient no. 020635) had no baseline scans; three patients (patient numbers 013672, 059733, 063682) may have had lesions that were irradiated.
5. Patients signed consent after enrollment but before start of study therapy.
6. Two additional patients (patient numbers 059645, 060653) had unspecified skin cancers.

Additionally, although no patients were considered to have significant cardiac abnormalities, several patients were enrolled in the study with a cardiac history that might be interpreted as significant (see Table 2).

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TABLE 2 SIGNIFICANT CARDIAC HISTORY

001617	MI, HTN, CABG, Pacemaker x2, valve replacement
001663	angina, CAD, hypercholesteremia, HTN, MI, rheumatic fever
013654	HTN, hypercholesteremia, DVT, ? CAD, ? MI, postop tachycardia
013737	chronic SVC thrombosis; peripheral RIJ thrombosis, right side chest pain consistent with chronic DVT; angioedema, retro cardiac density, mild HTN, cardiomegaly, hypercholesteremia, arrhythmia, varicose veins
020612	HTN, sinus tachycardia, atrial fib, tachycardia
035603	arrhythmia requiring pacemaker > IDC-S
035607	DVT (on PE)
035610	CAD, HTN, CABG
035628 ?	CAD, HTN, sick sinus syndrome, pacemaker, DVT, CABG
041702	CAD, CP, SOB, HTN, CABG
060604	HTN, CAD, CABG
060619	intraventricular conduction defect
060653	angina, HTN
060738	ASHD, CABG x4
061639	angina, CAD, CABG
061683	HTN, CAD, hypercholesteremia, angina, + stress test
061718	HTN, TIA
061734	HTN, hypercholesteremia, CAD
064677	HTN, CVA
065697	ventricular fibrillation, tachycardia
066632	Left anterior fascicular block, inferior infarct
066679	HTN, aortic stenosis, hypercholesteremia, cerebral artery occlusion, cerebral infarction, ischemic cerebrovascular disease
068724	HTN, CVA with L side deficits
020649	peripheral vascular dis, CAD, hypercholesteremia CABC, carotid endarterectomy
035685	arrhythmia
035725	cardiomegaly, atherosclerotics changes to aorta, prolonged QT
039662	TIA (CVS)
060623	at fib, PAT

Differences noted in yellow

In addition, ImClone notes 001611, 001669, 001710, 004687, ~~0736~~ 006719, 502695

2.1.1.2 Onstudy Irinotecan Dose

The protocol states, on page 18, Section 4.0 Study Design, "Irinotecan will be administered at the same regimen (dose/frequency) on which the patient became refractory to irinotecan therapy. Acceptable irinotecan regimens for this study are defined as: 350 mg/m^2 every 3 weeks (i.e., weeks 1 and 4); or 125 mg/m^2 weekly for 4 weeks followed by two weeks of rest", and on page 31, Section 9.2 Irinotecan Study Agent, "In this protocol irinctecan will be administered intravenously over 90 minutes at the same dosage regimen on which the patient became refractory to irinotecan therapy. Acceptable irinotecan dosage regimens for this study are: 350 mg/m^2 every 3 weeks (i.e., weeks 1 and 4); or 125 mg/m^2 weekly for 4 weeks followed by two weeks of rest. Irinotecan dose increases are not permitted on this study."

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TABLE 3 ON-STUDY IRINOTECAN DOSE DISCREPANCIES (BMS RESPONDERS HIGHLIGHTED)

Patient ID	Pre Study Dose (mg/m^2)	Pre Study Schedule	On Study Dose (mg/m^2)	On Study Schedule	Comments
001647	220	weekly	125	weekly	Pre study dose incorrectly entered in mg.
001669	200	database 3 weekly CRF weekly	125	weekly	Data entry error/Pre study incorrectly entered in mg.
001674	110	weekly	114	weekly	Minor
013672	104	weekly	108	weekly	Minor
013696	106	weekly	125	weekly	Protocol violation
020612	201	weekly	112	weekly	Pre study incorrectly entered in mg.
020633	250	3 weekly	125	weekly	Protocol violation
020649	157	3 weekly	350	3 weekly	Protocol violation/Pre study irinotecan in combination with 5-FU 285 mg/m^2
035610	87	weekly	88	weekly	Minor
035613	103	weekly	100	weekly	Minor
036678	87.5	weekly	74	weekly	Minor
041702	90	weekly	125	weekly	Protocol violation (time interval 4 weeks).
059642	71	weekly	72	weekly	Minor
060602	100	weekly	125	weekly	Protocol violation C1W1 (C1W2 100)
060623	125	weekly	68	weekly	"Dose reduced due to G4 diarrhea immediately prior to enrollment"
[redacted]					
[redacted]					
063682	107.6	weekly	100	weekly	Minor
064677	75	weekly	0	N/A	No irinotecan given C1W1 protocol violation
065697	50	weekly	125	weekly	Protocol violation. Pre study with 5 FU 600 mg weekly
065700	300	3 weekly	125	weekly	Protocol violation
066629	300	3 weekly	286	3 weekly	Minor
[redacted]					
066655	90 OR	weekly	343	3 weekly	Protocol violation, patient hospitalized with G3-4 AE's
066681	300	3 weekly	303	3 weekly	Minor
066698	125	weekly	108	weekly	Protocol violation
066693	533	weekly	67	weekly	Protocol violation
[redacted]					
[redacted]					
075735	100	weekly	125	weekly	Protocol violation
078664	125	weekly	75	weekly	Protocol violation
502666	225	weekly	125	weekly	Pre study likely incorrectly entered in mg. C1W1 delivered dose was 230 mg.

A total of 15 Protocol violations were found, in addition to minor variations such as apparent errors in units of pre study irinotecan (mg/m^2 required in CRF but mg likely entered), and a data entry error. Of the protocol violations, 3 involved responders; 061-718, 066-632, and 075-723.

✓ For Patient 061-718, the lower on study dose of irinotecan works against Erbitux so likely does not alter the value of the response.

✓ For patient 066-632, the regimen changed from weekly to three weekly. This change in schedule would not be expected to alter efficacy; however, the on study dose of irinotecan (275 mg/m^2) is lower than 350 mg/m^2 which is recommended by protocol, and is not justified by dose reductions in the weekly schedule pre study.

✓ For Patient 075-723, the irinotecan dose was increased from a pre study dose of 75 mg/m^2 to an on study dose of 125 mg/m^2. This change could have altered the response to irinotecan and could have an effect on the validity of this patient in the responder cohort.

2.1.1.3 Adverse Events Requiring Dose Modification

2.1.1.3.1 Cetuximab Dosing

The protocol states: "If a patient experiences a grade 3 skin toxicity (see Section 11.4, Definition of Grade 3 Skin Toxicity), Cetuximab therapy may be delayed for up to two consecutive infusions with no change in the dose level. The investigator also should consider concomitant treatment with topical and/or oral antibiotics; topical corticosteroids are not recommended. If the toxicity resolves to grade 2 or less by the following treatment period, treatment may resume. With the second and third occurrences of grade 3 skin toxicity Cetuximab therapy may again be delayed for up to two consecutive weeks with concomitant dose reductions to 200 mg/m^2 and 150 mg/m^2, respectively. Patient discontinuation will result if there are more than two consecutive infusions held or a subsequent occurrence of grade 3 skin toxicity." In the event that a patient experiences a Cetuximab related grade 4 toxicity, the patient will be discontinued from study.

NOTE: Cetuximab therapy will not be delayed for irinotecan-related toxicities, therefore, in the event that the next infusion of irinotecan is delayed, the patient will receive additional infusions of Cetuximab. All Cetuximab dosing delays mandate a hold on irinotecan dosing until treatment with Cetuximab is reinitiated. Patients will be discontinued from the study when Cetuximab therapy is discontinued.

If a patient develops an intercurrent illness (i.e., infection) that, in the opinion of the investigator and/or the PharmaNet Medical Monitor, mandates interruption of therapy, that intercurrent illness must resolve within a time frame such that no more than two consecutive infusions are withheld. In any case of delayed treatment, there will be no reloading dose, and all subsequent treatments will be at the assigned dose level. If therapy must be withheld for a longer period of time, the patient will be removed from the study, with the exception of a patient who is responding to therapy. In that case, the investigator may request that the patient continue to receive Cetuximab.

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TABLE 4 CETUXIMAB DOSING DEVIATIONS (PARTIAL LIST)

Patient No.	
001669 (FDA)	C2 - loading dose of 400 mg/m² was administered (6/12/00)
030618 (FDA)	Wrong dose was ordered for each infusion C1
059642 (FDA)	Grade 3 skin (rash): patient continued treatment with lower dose weeks 2, 4, 5, and 6 (dose should have been delayed until ≤ grade 2)
*001611	Grade 3 acne 05JAN00 - 14FEB00. Dose held 05JAN00 and 12JAN00; resumed dosing at 250 mg/m² on 19JAN00; patient should have been D/C — Do not agree
001636	Dose held C1, W3 - no reason given
*001669	Delay of 27 days between C1 and C2 due to grade 3 cellulitis (18MAY00 - 11JUN00); patient missed two consecutive infusions and should have been D/C unless patient was responding (17MAY00 scans did indicate that patient was responding).
001680	One week delay between C2 and C3 - no reason found.
*001692	Grade 3 acne 25MAY00 - 11DEC0; missed two infusions 25MAY00 (C1 W1-6, 2 missed), and 01JUN00 (C2 W1-9 1 missed), then 27JUL00 (patient was responding)
*001910	Grade 3 acne 06JUN00 - 18JAN01; missed infusions 02JUN00 - 14JUN00; 05JUL00 and 12JUL00 (lower dose 200 mg/m²); 09AUG00 (decreased dose 150 mg/m²)
004622	Grade 3 acne 07FEB00 - 28APR00; only one infusion held 11FEB00; dose was not decreased, patient was not discontinued. Day 11-92 grade 3 acne, pt D/C day 98
020612	20JAN00 C1 W3 (dose held) - no reason found — Not done
020624	Last two doses 08MAY00 and 15MAY00 were held - no AE reason. Patient withdrew consent = reason for discontinued — D/C pt withdrew consent Reason not Done. Should have received 5/8 D/C on 5/15
020635	10APR00 (C1 W7) was held because patient "ill:" per query 26JUN00 (C3 W5) patient cancelled appointment;- per query 03AUG00, 10AUG00 (C4 W3, W4) patient went to Africa.
020686	15MAY00 (C1 W3) no reason found 26JUN00 (C1 W8) query for missing CRFs but not for reason of delay 03JUL00 (C1 W9) no reason found C3 W 8, 9, 10 - doses held – no reason found
028681	19MAY00 (C1 W7) - the missing CRFs were queried but not the reason for drug delay 06JUL00 (C2 W7) - no reason found 29NOV00 (C6 W2) two weeks (13 days) between W1 and W2 - no reason found
*029704	13JUN00 - 20JUN00 (C1, W3 W4) – Grade 3 rash 13JUN00 - ongoing dose was never decreased (patient was responding, went on to receive 8 cycles)
035501	11NOV99 - CPT-11, 12NOV99 - C225 (C1, W6) - no reason found why dosing divided over two days.
035610	13JAN00 and 20JAN00 (C1 W5 W6) last two infusions before patient discontinued were held - no reason given – patient withdrew consent 27JAN00
035613	11FEB00 (C1 W7) dose held - per query – patient hospitalized (really C2 W1 delayed)
035728	

2.1.1.3.2 Irinotecan Dosing

Irinotecan hydrochloride is a commercially available antineoplastic agent for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following standard therapy. Investigators should use the approved irinotecan (Camptosar®) Package Insert for complete prescribing information such as dosage and administration, safety issues (warnings, precautions, adverse reactions, dose modifications and omissions, and storage information. Investigators should also follow institutional procedures for the administration of irinotecan.

In this protocol irinotecan will be administered intravenously over 90 minutes at the same dosage regimen on which the patient became refractory to irinotecan therapy. Acceptable irinotecan dosage regimens for this study are: 350 mg/m^2 every 3 weeks (i.e., weeks 1 and 4); or 125 mg/m^2 weekly for 4 weeks followed by two weeks of rest. Irinotecan dose increases are not permitted on this study. Irinotecan will be infused one hour following the completion of the Cetuximab infusion.

The Camptosar package insert states the following:

Dosage Regimens

CAMPTOSAR should be administered as an intravenous infusion over 90 minutes for both the weekly and once-every-3-week dosage schedules (see Preparation of Infusion Solution). Single-agent dosage regimens are shown in Table 12.

A reduction in the starting dose by one dose level of CAMPTOSAR may be considered for patients with any of the following conditions: age >/=65 years, prior pelvic/abdominal radiotherapy, performance status of 2, or increased bilirubin levels. Dosing for patients with bilirubin >2 mg/dL cannot be recommended since such patients were not included in clinical studies.

It is recommended that patients receive premedication with antiemetic agents. Prophylactic or therapeutic administration of atropine should be considered in patients experiencing cholinergic symptoms. See PRECAUTIONS, General.

Dose Modifications

The protocol states the following: Patients should be carefully monitored for toxicity and doses of CAMPTOSAR should be modified as necessary to accommodate individual patient tolerance to treatment. Based on recommended dose-level, described in Table 12, Single-Agent Regimens of CAMPTOSAR and Dose Modifications, subsequent doses should be adjusted as suggested in Table 13, Recommended Dose Modifications for Single-Agent Schedules.

All dose modifications should be based on the worst preceding toxicity.

A new course of therapy should not begin until the toxicity has recovered to NCI grade I or less. Treatment may be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicity. If the patient has not recovered, consideration should be given to discontinuing this combination therapy. Provided intolerable toxicity does not develop, treatment with additional courses of CAMPTOSAR may be continued indefinitely as long as patients continue to experience clinical benefit.

The package insert states the following:

TABLE 5 SINGLE-AGENT REGIMENS OF CAMPTOSAR AND DOSE MODIFICATIONS

	125 mg/m² IV over 90 min, d 1, 8, 15, 22 then 2-wk rest Starting Dose & Modified Dose Levels[2] (mg/m²)		
Weekly Regimen[1]	Starting Dose	Dose Level –1	Dose Level -2
	125	100	75
	350 mg/m² IV over 90 min, once every 3 wks[3] Starting Dose & Modified Dose Levels (mg/m²)		
Once-Every-3-Week Regimen[1]	Starting Dose	Dose Level –1	Dose Level -2
	350	300	250

1. Subsequent doses may be adjusted as high at 150 mg/m² or to as low as 50 mg/m² in 25 to 50 mg/m² decrements depending upon individual patient tolerance.
2. Subsequent doses may be adjusted as low as 200 mg/m² in 50 mg/m² decrements depending upon individual patient tolerance.
3. Provided intolerable toxicity does not develop, treatment with additional courses may be continued indefinitely as long as patients continue to experience clinical benefit.

TABLE 6 RECOMMENDED DOSE MODIFICATIONS FOR SINGLE-AGENT SCHEDULES[1]

A new course of therapy should not begin until the granulocyte count has recovered to >/= 1500/mm³, and the platelet count has recovered to >/=100,000/mm³, and treatment-related diarrhea is fully resolved. Treatment should be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicities. If the patient has not recovered after a 2-week delay, consideration should be given to discontinuing CAMPTOSAR.

Worst Toxicity NCI Grade[1](Value)	During A Course of Therapy	At the Start of the Next Courses of Therapy (After Adequate Recovery), Compared with the Start Dose in the Previous Course[1]	
	Weekly	*Weekly*	*Once Every 3 Weeks*
No Toxicity	Maintain Dose Level	Up 25 mg/m² up to a maximum dose of 150 mg/m²	Maintain dose level
Neutropenia			
1 (1500 to 1999/mm³)	Maintain Dose Level	Maintain Dose Level	Maintain Dose Level
2 (1000 to 1499/mm³)	down 25 mg/m²	Maintain Dose Level	Maintain Dose Level
3 (500 to 999/mm³)	Omit dose, then down 25 mg/m² when resolved to </= grade 2	down 25 mg/m²	Down 50 mg/m²
4 (<500/mm³)	Omit dose, then down 50 mg/m² when resolved to </= grade 2	down 50 mg/m²	Down 50 mg/m²
Neutropenic Fever			
(grade 4 neutropenia & >/= grade 2 fever)	Omit dose, then down 50 mg/m² when resolved	down 50 mg/m²	Down 50 mg/m²
Other hematologic toxicities	Dose modification for leukopenia, thrombocytopenia, and anemia during a course of therapy and at the start of subsequent courses of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above		
Diarrhea			
1 (2-3 stools/day > pretx[1])	Maintain Dose Level	Maintain Dose Level	Maintain Dose Level
2 (4-6 stools/day > pretx)	down 25 mg/m²	Maintain Dose Level	Maintain Dose Level
3 (7-9 stools/day > pretx)	Omit dose, then down 25 mg/m² when resolved to </= grade 2	down 25 mg/m²	Down 25 mg/m²
4 (>/= 10 stools/day > pretx)	Omit dose, then down 50 mg/m² when resolved to </= grade 2	down 50 mg/m²	Down 50 mg/m²
Other nonhematologic toxicities			
1	Maintain Dose Level	Maintain Dose Level	Maintain Dose Level
2	down 25 mg/m²	down 25 mg/m²	Down 50 mg/m²

Worst Toxicity NCI Grade[2](Value)	During A Course of Therapy	At the Start of the Next Courses of Therapy (After Adequate Recovery), Compared with the Start Dose in the Previous Course[1]	
	Weekly	*Weekly*	*Once Every 3 Weeks*
3	Omit dose, then down 25 mg/m² when resolved to <= grade 2	down 25 mg/m²	Down 50 mg/m²
4	Omit dose, then down 50 mg/m² when resolved to <= grade 2	down 50 mg/m²	Down 25 mg/m²

1. All dose modifications should be based on the worst preceding toxicity.
2. National Cancer Institute Common Toxicity Criteria
3. Pretreatment

A complete review of irinotecan dose modification was not performed. Cases were observed where irinotecan was delayed for grade 2 diarrhea rather than continuing with a 25 mg/m² dose reduction as recommended in the package insert. Since the details of irinotecan dose modification were not specified in the protocol, it can be assumed that less attention was paid to this during study monitoring. In addition the AE page does not include the relationship of the AE to irinotecan, but is headed "Relationship to Cetuximab." The protocol allows Cetuximab to continue although irinotecan is held. It appears that the investigators assumed that myelosuppression and diarrhea were related to irinotecan rather than Cetuximab. Frequently investigators delayed weekly irinotecan doses rather than omitting doses as recommended by the package insert. It does not appear that these issues lead to safety problems in this study. Further investigation into community practice with weekly irinotecan might confirm that oncologists were dose modifying according to usual community practice standards.

2.1.1.6 Completeness of Baseline and On-study Evaluations

2.1.1.6.1 On Study Assessments

As cited by the FDA, patient 020-635 entered the study without metastatic disease and remained on study in the absence of metastatic disease until withdrawing consent.

No other such cases have been found.

2.1.1.6.2 Tumor Measurements

In several patients, the totality of metastatic disease is not captured on the tumor measurement page. An example is 061-644. In this case, the Evaluable Disease Response has been left blank with no apparent data queries. This represents incomplete data

monitoring. However would not have compromised the primary endpoint if the IRAC procedure was well performed.

2.1.2 IMCL CP02-9923 Refractoriness to Irinotecan and Efficacy

2.1.2.1 BMS Response Assessment

A review of a listing containing dates of radiologic evaluation, bidimensional measurements and sum of products for all measurable lesions, sites of measurable and evaluable disease, presence of new lesions, and indication of change in status of evaluable disease was independently reviewed by two BMS personnel. Response was characterized by evaluating the sum of products for all lesions (not by individual lesion) according to the following definitions:

Complete response (CR): Complete disappearance of all tumor lesions for at least four weeks from the date of documentation of complete response.

Partial response (PR): Decrease by 50% or greater in the sum of the products of the two largest perpendicular diameters of all measurable lesions as determined by two consecutive observations at least four weeks apart. A decrease by 50% or greater is also required for unidimensional lesions. No lesions, measurable or not, should have progressed and no new lesions should appear.

Stable disease (SD): Failure to observe responses as defined above, in the absence of any progressive or new lesions, as determined by two consecutive observations at least four weeks apart.

Progressive disease (PD): At least 25% increase in the size of any measurable or evaluable lesion and/or the appearance of any new lesions or the occurrence of a malignant pleural effusion or ascites.

Following independent assignment of response by each reviewer, any difference in assessment between the reviewers was adjudicated and agreed to by both reviewers, and the information was collected on a CRF page signed by both reviewers.

2.1.2.2 Review of Final Study Report

2.1.2.2.1 Summary of evidence of patient refractoriness to irinotecan in IMCL CP02-9923

The following summarizes data available within the BLA submitted to the FDA for patients enrolled on study IMCL CP02-9923 (Phase II Study of an Anti-Epidermal

Growth Factor Receptor (EGFR) Antibody, Cetuximab, in Combination with Chemotherapy in Patients with Advanced Colorectal Carcinoma).

2.1.2.2.2 METHODS

2.1.2.2.2.1 DATA REQUIREMENTS TO DEMONSTRATE WHETHER PATIENTS WERE REFRACTORY TO PRIOR THERAPY

At a minimum, we believe we need the following datapoints for the last irinotecan containing regimen administered to establish whether a patient was refractory to the irinotecan containing regimen:

- Schedule of administration (weekly or q 3 weeks)
- Dose
- Start date
- Stop date
- Reason the patient stopped treatment
- The best response to the irinotecan containing regimen and the date of response
- Answer to the question "Did the patient progress while receiving last irinotecan regimen?"
- Date of progression

Separately, and in addition, based on the successful filing of CPT11 in 5FU refractory colorectal cancer, for responding patients we feel we should create an auditable database of available scans, scan reports, and clinical notes for an Independent Review by a committee of 2 medical oncologists and 2 radiologists.

If refractoriness to prior fluoropyrimidine containing therapy must also be proven, the same data would need to be collected for prior fluoropyrimidine containing therapy.

2.1.2.2.2.2 DATA REVIEWED

There are few data present in the BLA database upon which to judge whether a patient was refractory to irinotecan. Only two pages of the CRF collected relevant data. The following is a list of the seven datapoints collected in the CRF which might help determine whether a patient had irinotecan-refractory disease at the time of enrollment into the study.

1. On the CRF page titled ENROLLMENT CRITERIA, under the heading INCLUSION CRITERIA: *ALL MUST BE CHECKED YES TO BE ELIGIBLE*, the question in version 1 of the CRF is:

   - "Patient must have demonstrated progression of disease after completing two courses of a regimen containing irinotecan". Accepted answers are YES or NO.

The question in version 2 of the CRF is:

- "Patient has documented stable disease (must have received a minimum of 12 weeks of irinotecan therapy) or progressive disease at any time after receiving an irinotecan-containing regimen. Copies of scans must be provided to confirm the lack of objective response to prior therapy". Accepted answers are YES or NO.

2. On the CRF page titled PREVIOUS IRINOTECAN THERAPY and OTHER PREVIOUS THERAPY, the following data are captured for the previous irinotecan therapy:

   - a box to record DOSE
   - a box to record REGIMEN, with options to check a box for WEEKLY or Q3WEEKS
   - a fill-in-the-blanks space to record DATE STARTED M/D/Y
   - a fill-in-the-blanks space to record DATE ENDED M/D/Y
   - a box to record RESPONSE, with options to record STABLE DISEASE OR PROGRESSIVE DISEASE (no other options given)
   - a fill-in-the-blanks space to record DATE OF RESPONSE M/D/Y
   - the date of progression to prior irinotecan containing treatment can not be definitively determined from this information

Patient data listings and CRFs contained within the Clinical Study Report of the BLA were reviewed. Based on the data requirements to establish refractoriness to prior therapy listed above, and the information contained within the BLA, it is evident that the BLA contains insufficient data to definitively establish refractoriness to prior irinotecan therapy for patients enrolled on IMCL CP02-9923.

2.1.2.2.3 RESULTS

2.1.2.2.3.1 PATIENT SUBSETS

One hundred thirty-eight patients received C225 and irinotecan in this trial.

The datapoints recording date of response on the previous irinotecan prior therapy CRF (with the 2 options for response being stable disease and progressive disease) does not allow the definitive determination of the date of progression to irinotecan. Instead, subsets of patients with a defined interval between the stop date of previous irinotecan therapy and the start date of C225 are provided.

The investigator judged the best response to the most recent irinotecan-containing regimen as progressive disease in 114 of the 138 C225 and irinotecan-treated patients. For these 114 patients, the median duration between the most recent irinotecan administration and the start of C225 treatment was 1.2 months (range 0.3 to 12.0 months). The interval between most recent irinotecan administration and the start of C225 was ≤ 3 months in 100 patients, ≤ 1.5 months in 71 patients, and ≤ 1.0 months in 47 patients.

The number of patients with BMS objective tumor responses in these patient subsets are listed in the table below:

TABLE 7 PATIENTS WITH BMS OBJECTIVE TUMOR RESPONSES ACCORDING TO PATIENT SUBSETS

CRF response to most recent irinotecan	Duration since the most recent irinotecan (months)	Number of patients in subgroup	Number of BMS responses in subgroup (%) [95% CI]	Number of BMS responses with prior 5-FU (%) [95% CI]
any	any	138	27 (19.6) [13.3-27.2]	25 (18.1) [12.1-25.6]
PD	any	114	20 (17.5) [11.1-25.8]	19 (16.7) [10.3-24.8]
PD	≤ 6.0 months	108	19 (17.6) [10.9-26.1]	18 (16.7) [10.2-25.1]
PD	≤ 3.0 months	100	17 (17.0) [10.2-25.8]	16 (16.0) [9.4-24.7]
PD	≤ 2.0 months	86	12 (14.0) [7.4-23.1]	11 (12.8) [6.6-21.7]
PD	≤ 1.5 months	71	12 (16.9) [9.1-27.7]	11 (15.5) [8.0-26.0]
PD	≤ 1.0 month	47	6 (12.8) [4.8-25.7]	5 (10.6) [3.6-23.1]

2.1.2.2.3.2 EVIDENCE FOR OBJECTIVE TUMOR RESPONSE

Following BMS response assessment, 27 patients of the 138 C225 and irinotecan-treated patients were judged as having an objective tumor response. Among the 114 patients with progressive disease following the most recent irinotecan-containing regimen, 20 patients (17.5%) were judged as having an objective tumor response. Objective responses occurred in 17 of 100 patients (17.0%) with an interval between the stop date of irinotecan and the start of C225 of ≤ 3 months, in 12 of 86 patients (14.0%) with an interval of ≤ 2 months, in 12 of 71 patients (16.9%) with an interval of ≤ 1.5 months, and in 6 of 47 patients (12.8%) with an interval of ≤ 1 month. Three patients with an objective response had intervals of > 3 months duration. Of these, two patients (intervals of 3.2 months and 7.8 months) had no intervening therapy, and one patient (interval of 4.6 months) received intervening radiation therapy.

There was complete concordance between the derived Investigator Response and BMS Response. Individual responders are described in the table below.

TABLE 8 RESPONDERS - IMCL CP02-9923 (BMS RESPONSE): PROGRESSIVE DISEASE COHORT[1]

Patient ID	Last Regimen	Duration of Last Irinotecan (weeks)	CRF Final Outcome of Irinotecan	Months from Last Irinotecan to first C225	Response Duration (months)	Comments	Prior 5 FU
043 657	Irinotecan weekly	57.1	PD	0.69	5.6		Yes
061 718	Irinotecan weekly	9.1	PD	0.69	4.9	Confirmed by BMS due diligence	Yes
066 632	Irinotecan/ Xeloda	24.4	PD	0.92	6.9	Prior panorex and oxaliplatin. Confirmed by BMS due diligence	Yes
061 683	Irinotecan alone	12.1	PD	0.92	3.0	Failed XRT/5FU within 4 months, Stage D at diagnosis. Confirmed by BMS due diligence	Yes
068 724	Irinotecan alone	12.3	PD	0.92	6.9+	Confirmed by BMS due diligence	No
013 737	Irinotecan alone weekly	14.7	PD	0.95	2.7	Confirmed by BMS due diligence	Yes
066 708	Irinotecan/ 5 FU/LV	9.0	PD	1.15	3.0	Prior oxaliplatin & irinotecan/Xeloda. BMS due diligence showed SD	Yes
061 615	Irinotecan alone	3.1	PD	1.15	7.0	Confirmed by BMS due diligence	Yes
066 679	Irinotecan alone	4.1	PD	1.18	8.7	Dukes C at diagnosis 5 FU ended by 1996 so adjuvant failure >1 mos. after completion - prior oxaliplatin	Yes
060 738	Irinotecan alone	34.0	PD	1.18	2.9	Prior prostate cancer (1994) treated with Lupron & XRT (1997), rectal cancer 1996. BMS due diligence showed SD	Yes Given with XRT
020 627	Irinotecan alone weekly	30.0	PD[7]	1.31	8.3	Confirmed by BMS due diligence	Yes
028 661	Irinotecan/ 5 FU/LV	41.0	PD	1.45	3.5	Confirmed by BMS due diligence	Yes

Patient ID	Last Regimen	Duration of Last Irinotecan (weeks)	CRF Final Outcome of Irinotecan	Months from Last Irinotecan to first C225	Response Duration (months)	Comments	Prior 5 FU
043 643	Irinotecan alone	19.7	PD	2	1.4	Prior oxaliplatin. Confirmed by BMS due diligence	Yes
075 723	Irinotecan/ 5 FU/LV	35.1	PD	2.14	9.5	Confirmed by BMS due diligence	Yes
502 699	Irinotecan alone weekly	22.9	PD	2.27	2.6	Confirmed by BMS due diligence	Yes
502 715	Irinotecan alone	49.1	PD	2.76	4.8	Confirmed by BMS due diligence	Yes
061 644	Irinotecan alone	101.1	PD	2.3	8.5	Dukes B at diagnosis 5 FU/LV ended by 1996. Likely adjuvant.	Yes
059 665	Irinotecan alone	34.3	PD	3.19	6.0		Yes
060 621	Irinotecan alone	10.1	PD	4.6	2.6	Confirmed by BMS due diligence	Yes
063 648	Irinotecan alone	43.1	PD	7.79	2.3	Adjuvant 5 FU/LV for Dukes C with progression > 1 year	Yes

1. Additional PD cohort (CRF) Responders, BMS due diligence: 013737, 059730, 061683, 068673.
2. Data entry error, PD according to Query.

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TABLE 9 OF RESPONDERS - IMCL CP02-9923 (BMS RESPONSE): STABLE DISEASE COHORT[1]

Patient ID	Last Regimen	Duration of Last Irinotecan (weeks)	CRF Final Outcome of Irinotecan	Months from Last Irinotecan to First C225	Response Duration (months)	Comments	Prior 5 FU
066 731	Irinotecan alone	3.1	SD	0.62	3.0	BMS due diligence showed SD	Yes
029 704	Irinotecan alone weekly	14.0	SD[2]	0.66	8.3+	CRF SD, Database PD data entry error. Confirmed by BMS due diligence	No
035 728	Irinotecan alone	9.1	SD	0.69	7.8	Prior oxaliplatin	Yes
020 649	CPT 11/5 FU every 3 weeks	12.0	SD	0.76	6.9		Yes
020 624	CPT 11 alone weekly	10.1	SD	1.05	3.0	Confirmed by BMS due diligence	Yes
066 714	Irinotecan alone	34.9	SD	1.15	6.9		No
060 619	Irinotecan/ 5 FU/LV	25.3	SD	3.02	7.2	BMS due diligence showed SD	Yes

1. Additional SD cohort (CRF) Responders, BMS due diligence: 020686, 035685, 060614.
2. Data entry error, SD in CRF but database shows PD.

2.1.3 IMCL CP02-9923 Safety

2.1.3.1 Study 9923 Deaths

Data regarding patient death can be obtained from the REPORT OF PATIENT DEATH and SURVIVAL FOLLOW-UP CRF pages.

1. The following are captured on the REPORT OF PATIENT DEATH CRF page:

- The question DID PATIENT DIE WITHIN 30 DAYS OF DISCONTINUATION OF THERAPY?, with an option to check a box marked YES or NO;
- For a YES answer, the DATE OF PATIENT DEATH is to filled in a fill-in-the-blanks space to record M/D/Y;
- The question WHAT WAS THE PRIMARY CAUSE OF DEATH?, with options to check a box for DISEASE PROGRESSION, DISEASE-RELATED COMPLICATION, INTERCURRENT OR UNRELATED ILLNESS/EVENT, EVENTS RELATED TO CETUXIMAB, EVENTS RELATED TO CHEMOTHERAPY, or UNKNOWN.

2. The following are captured on the relevant portion of the SURVIVAL FOLLOW-UP CRF page:

- The question IS THE PATIENT STILL ALIVE?, with the option to check a box marked YES or NO;
- The question IF THE PATIENT DIED, WHAT WAS THE DATE OF DEATH?, with in a fill-in-the-blanks space to record M/D/Y.

Within the BLA, patient narratives are only provided for patients who died within 30 days of treatment discontinuation for reasons other than disease progression, rather than for all patients. Nineteen patients are identified as having died within 30 days of discontinuation in Study 9923. Of these, three patients are stated to have died for reasons other than disease progression, and only narratives for these patients (patient numbers 061-631, 066-689, and 502-715) are included in the BLA. The 19 patients were identified from the "patient deaths within 30 days of last infusion" data listing.

Review of the "survival follow-up" data listing reveals three additional patients who died within 30 days of the last treatment (patient numbers 020-612, 059-642, and 063-638), increasing the total to 22 patients who died within 30 days of treatment discontinuation.

2.1.3.2 Study 9923 Hospitalizations

Data on hospitalizations can only be discerned from the ADVERSE EVENTS END OF COURSE CRF. For a given adverse event, under ACTION TAKEN, code # 4 signifies NEW OR

PROLONGED HOSPITALIZATION. No other fields are available to record the details of the hospitalization.

A total of 62 patients were identified who had at least one episode of hospitalization not specifically required by the protocol. From the data available it is possible to identify the reason for hospitalization, the number of hospitalizations per patient, but not the duration of hospitalization. Patient narratives are not provided on all hospitalizations not specifically required by the protocol.

2.1.3.3 Study 9923 Discontinuations: Inconsistencies And Discrepancies That Impact On The Interpretation Of The Toxicity Profile

Preliminary review of the data listings, CRFs, and reports indicate that are inconsistencies that may impact the assessment of the toxicity profile. For example, patients 001-680 and 020-635 are listed in the database as coming off study because of having withdrawn consent. Both patients have numerous adverse events listed with associated use of concomitant medications throughout the study period, and the reason for discontinuation is not queried. In addition, patient 020-624 is also identified as having discontinued because of consent withdrawal. This patient also has a number of adverse events listed in the CRF page, and a query of the reason for discontinuation generated on 14FEB01 states that the patient "withdrew consent due to the following adverse events." However, the database was not corrected, and the patient is still listed as having withdrawn consent.

In summary, additional narratives for all patient deaths, discontinuations, and serious adverse events will be required. Preliminary review of the SAE reports recently received from ImClone Systems Inc. appear to be sufficient to evaluate the cases in detail for the purpose of writing the narratives. However, additional information may be required once the review is undertaken. Additional data collection will be required to complete narratives for all hospitalizations.

2.1.4 IMCL CP02-9923 QOL Assessment

The 9923 clinical study used the FACT-C Questionnaire as the QOL instrument to assess the impact of adding Cetuximab to existing therapy of irinotecan for patients with recurrent or metastatic colorectal carcinoma. The protocol states that the evaluation of QOL is a secondary objective of the study and analysis will be exploratory and noncomparative. The QOL instrument will be completed by the patient at baseline, at the completion of every 6 week course, at the time of post-treatment assessments, and during follow-up assessments. QOL assessment was according to the FACIT scoring manual. Additionally, the protocol states that "Compliance with completion of the QOL assessments will be reviewed frequently." Of concern is the allowance for patients to take the questionnaire home and complete it at a later time.

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Of the 138 intent-to-treat population the following is a break-down of the completion of the QOL instrument:

N=138	Baseline	End of Patients' Last Cycle	Follow-up
Completed Questionnaire FACT-G	135	77	44
Completed Questionnaire FACT-C	133	To be determined	To be determined

Given the real-time nature of the instrument completion we are unable to retrieve missing instrument data (this would involve patients completing the questionnaire for the missing assessment points).

The final study report recorded QOL evaluations for each study group (PD/SD) and in aggregate, by instrument (FACT-G) and Total FACT-C scoring, as well as by subscale: physical well being, social/family well being, emotional well-being, functional well being, and additional concerns. The analyses were completed for the intent-to-treat population, at each assessment timepoint (end of each course and follow-up), and as an aggregate of change from baseline.

Per Table 9.17 in the final study report of 9923 the mean change from baseline for the FACT-G was –3.58 (12.915) and the Total FACT-C Score was –4.28 (15.751). The negative findings reflect a worsening of QOL. These results identify the aggregate result of all patients who completed the baseline assessment and one additional questionnaire, which could have been different than their last cycle or follow-up questionnaire. (For the 75 patients who did not complete a QOL instrument at discontinuation of their last cycle, the questionnaire used was from a previous cycle or follow-up.)

The report did not analyze longitudinal findings based on changes from baseline and questionnaire completed at patient's last cycle or baseline to follow-up. Additionally, subset analyses on responders was not completed. We would recommend further analyses completed on these parameters as well as additional subsets.

2.1.5 IMCL CP02-9923 Data Entry Review

Audit Summary for IMCL CP02-9923

A CRF (including query forms) versus database audit was conducted by BMS Data Management on Jan 8 and Jan 9, 2002. For the 139 patients for which CRFs were provided, Level 1 variables were checked. For the 27 randomly selected patients, Level 2 variables were checked. The randomly selected patients and the variables selected for auditing were determined by the BMS statistician. Listings were generated by BMS statistical and programming staff and were based on the raw database values. The two levels are as follows:

Level 1 – Critical Variables (138 patients)	Tumor Measurements (all lesions - all courses including baseline) Measurement Date, Lesion Site Text, Measurable/Evaluable Indicator, First Measurement, and Second Measurement
Level 2 – Important Variables (27 patients)	Adverse Event (all adverse events) AE Text, Onset Month, Onset Day, Onset Year, Resolution onth, Resolution Day, Resolution Year, Toxicity Grade, and SAE indicator Study Drug Administration Dosing Month, Dosing Day, Dosing Year, Study Drug Name, Test Dose, and Dose Level Discontinuation Discontinuation Reason Report of Patient Death Death Within 30 Days question, Death Month, Death Day, Death Year, and Cause Previous Irinotecan Therapy Start Date and Stop Date Other Previous Therapy Therapy Text, Dosage, Start Month, Start Day, Start Year, Stop Month, Stop Day, Stop Year, Progression Month, Progression Day, Progression Year

Findings:

Denominators were estimated based on the average number of datapoints for the variables for the patients being audited. Any datapoint which was different from the documentation found in the CRFs provided was counted as an error. Please note that this includes datapoints in the database for which no CRF page could

be found.

	Total Errors/Estimated Total Datapoints	Error Rate
Level 1 - Tumor Meas.	2 /8004	0.02%
Level 2 - Adverse Event	67 /8397	0.79%
- Dosing	0 /540	0.00%
-Discontinuation	0 /139	0.00%
-Death	0 /139	0.00%
-Prev. Irinotecan	20 /216	9.26%
-Other Previous	99 /2970	3.33%

Note: Acceptable error rates for BMS studies managed by BMS Data Management are 0.0% error rate for
Level 1 variables and less than 0.5% for Level 2 variables.

Comments:

Randomly selected patients for the Level 2 audit were: 001-636, 013-626, 020-612, 020-624, 028-661, 035-603, 035-606, 035-685, 035-728, 036-701, 059-730, 060-614, 060-653, 060-738, 061-637, 061-709, 061-736, 063-638, 063-648, 065-697, 065-717, 066-629, 066-689, 066-703, 066-732, 068-724, 502-715.

Documentation of these discrepancies will be kept in the Data Management Study folder for this study.

2.2 IMCL CP02-0141

2.2.1 IMCL CP02-0141 PROTOCOL VIOLATIONS

Summary of findings regarding protocol violations in study IMCL CP02-0141 (Phase II Study of an Anti-Epidermal Growth Factor Receptor (EGFR) Antibody, Cetuximab, in Patients with Irinotecan-Refractory, Stage IV Colorectal Carcinoma) for eligibility, dosing and dose modification.

The following summarizes findings within the BLA and patient CRFs with regard to protocol violations including violations of eligibility, dose modification and study procedures for response determination.

2.2.1.1 Methods

The protocol was reviewed to identify protocol requirements regarding eligibility, dosing and dose modification as listed below. Subsequently, data listings from the IMCL CP02-0141 Clinical Study Report were reviewed to identify incidences of protocol violation. These data listings are listed below.

2.2.1.2 Protocol Requirements

2.2.1.2.1 Eligibility

The protocol eligibility criteria were reviewed and violations were identified using data in the IMCL CP02-0141 Clinical Study Report (specifically, Appendix 15.2, listing 05).

2.2.1.2.2 Schedule of Drug Administration

The protocol requires 6 weekly cetuximab infusions per course, administered within ± 1 day of the weekly schedule.

2.2.1.2.3 Dose Modification for Adverse Events

With regard to dose modification for acne, the protocol specifically required the following:

- for the first incidence of grade 3 skin toxicity, Cetuximab infusion may be delayed for up to two consecutive weeks with no change in dose; treatment may resume if the skin toxicity resolves to grade 2 by the next treatment cycle

- for the second and third occurrences of grade 3 skin toxicity, Cetuximab infusion may be delayed for up to two consecutive weeks with a dose reduction to 200 and 150 mg/sqm, respectively;
- dose reductions are permanent
- discontinuation of a patient if more than two consecutive infusions are held (ie, greater than 2 week dose delay) or a subsequent (fourth) occurrence of grade 3 skin toxicity
- occurrence of any grade ≥ 3 skin toxicity required a dermatological consultation, including photos of the skin toxicity at the time of the grade 3 reaction and upon resolution

With regard to dose modification for allergic reactions, all patients experiencing a grade 3 allergic or grade 4 anaphylactic reaction were to be discontinued from the study.

With regard to dose modification for all other adverse events, there are no specific dose modification rules stated. The protocol allowed for a delay of up to two consecutive infusions (ie, 2 weeks) for patients who developed "an intercurrent illness (ie, infection) that, in the opinion of the investigator and/or medical monitor" mandated the interruption of therapy. The investigator was instructed to "use judgment in determining which treatment alterations" were best suited for the patient. Treatment delays of more than two consecutive infusions in patients responding to therapy were allowed only with Sponsor approval.

2.2.1.2.4 Data Listings Reviewed

Tables and Data Listings from the BLA and relevant patient CRFs were reviewed to make the determination of whether or not a patient's eligibility, dosing, and dose modifications constituted a protocol violation. The following Tables and Data Listings were reviewed:

1. Table 5.2 (Patient Drug Exposure by Dose)
2. Table 7.4 (Patients with Dose Modification for Toxicities)
3. Table 6.2 (Adverse Events by Body System)
4. Appendix 15.2, Data Listing 14 (Study Drug Administration)
5. Appendix 15.2, Data Listing 03 (Enrollment Criteria)

2.2.1.2 RESULTS

2.2.1.2.1 Eligibility Criteria Violations

Two patients were given a protocol exemption to enroll in IMCL CP02-0141 despite failing to meet protocol eligibility criteria number 2 ("The patient has documented progressive disease ≤ 6 months after receiving an irinotecan-containing regimen"). Patient (003-1121) had progressed 6.3 months following last irinotecan administration and did not respond to C225. Patient 002-1143 had progressed 10.6 months following last irinotecan administration.

2.2.1.2.2 Dose Administration

Among the 57 patients treated with C225 in this trial, one patient was found to have received an incorrect dose of C225. Patient 061-1102 received 251 mg/m^2 during cycle 1, week 2. This was queried, and the pharmacy confirmed that 251 mg/m^2, not 250 mg/m^2, was administered.

Patient ID	Incorrect Dose Administered
061-1102	07 May 01 (C1W2) dose administered at 251 mg/m^2

Additionally, 12 patients received a total of 16 C225 infusions where the treatment date was two or more days different from the ideal weekly treatment date. All variations from the ideal weekly treatment date were delays. The median delay was two days (range 2 - 7 days). Six patients received six treatments that were ≥ three days delayed. No delays were related to toxicity.

Patient ID	Treatment deviated from weekly schedule ≥ 2 days
001-1128	20 Jul 01 (C1W5) dose administered more than ± 1 day from appropriate date (2 days late) - no reason provided in CRF
001-1129	11 Jul 01 (C1W4) dose administered more than ± 1 day from appropriate date (2 days early) due to July 4th holiday
001-1132	06 Jul 01 (C1W2) dose administered more than ± 1 day from appropriate date (2 days late) due to scheduling and holiday 11 Jul 01 (C1W3) dose administered more than ± 1 day from appropriate date (2 days early) due to scheduling and holiday
002-1144	23 Aug 01 (C2W1) dose administered more than ± 1 day from appropriate date (3 days late) - no reason provided in CRF
002-1151	21 Aug 01 (C2W1) dose administered more than ± 1 day from appropriate date (2 days early) - no reason provided in CRF
003-1121	25 Jun 01 (C1W2) dose administered more than ± 1 day from appropriate date (3 days late) - no reason provided in CRF
003-1157	23 Jul 01 (C1W2) dose administered more than ± 1 day from appropriate date (4 days late) due to scheduling
003-1158	23 Jul 01 (C1W2) dose administered more than ± 1 day from appropriate date (3 days late) - no

	reason provided in CRF
061-1101	04 Sep 01 (C4W1) dose administered more than ± 1 day from appropriate date (5 days late) due to scheduling of the CT scan appointment for C3 13 Sep 01 (C4W2) dose administered more than ± 1 day from appropriate date (2 days late) due to WTC disaster
061-1103	09 May 01 (C1W2) dose administered more than ± 1 day from appropriate date (2 days late) due to constipation (grade unknown - CRFs provided in this file were for patient 061-1104) 31 May 01 (C1W5) dose administered more than ± 1 day from appropriate date (3 days late) because patient felt very fatigued (grade unknown – CRFs provided in this file were for patient 061-1104) and could not come in to get chemo
061-1111	02 Jul 01 (C2W1) dose administered more than ± 1 day from appropriate date (2 days early) - no reason provided in CRF 05 Sep 01 (C3W4) dose administered more than ± 1 day from appropriate date (2 days late) due to holiday scheduling 10 Sep 01 (C3W5) dose administered more than ± 1 day from appropriate date (2 days early) due to holiday scheduling
061-1125	18 Sep 01 (C3W1) dose administered more than ± 1 day from appropriate date (7 days late) - no reason provided in CRF

2.2.1.2.3 Dose Modifications

2.2.1.2.3.1 DOSE DELAY FOR SKIN TOXICITY

Fifteen patients had at least one weekly infusion held due to grade 3 skin toxicity (7 patients) or intercurrent illness (8 patients). These dose delays are considered to have been made according to the protocol-defined criteria. In no case was the C225 treatment held for more than two consecutive weekly infusions.

Patient ID	Dose Delays for Skin Toxicity
001-1133	05 Jul 01 (C1W2) dose held 1 week due to Gr 3 acne-like rash
001-1138	17 Jul 01 (C1W3) dose held 1 week due to Gr 3 acne-like rash
001-1153	25 Jul 01 (C1W3) dose held 1 week due to Gr 1/2 possible cervical neck abscess
001-1160	27 Jul 01 (C1W3) dose held 1 week due to Gr 3 skin toxicity
002-1123	10 Jul 01 (C1W4) dose held 1 week due to Gr 3 hypoxia
002-1144	23 Jul 01 (C1W3) dose held due to Gr 3 skin toxicity
002-1156	27 Jul 01 (C1W3) and 03 Aug 01 (C1W4) doses held due to patient hospitalization
003-1121	04 Sep 01 (C2W6) dose held due to Gr 3 rash
003-1124	10 Jul 01 (C1W4) and 17 Jul (C1W5) doses held due to patient hospitalization for small bowel obstruction
061-1102	21 May 01 (C1W4) dose held due to abnormal bilirubin
061-1104	21 Jun 01 (C1W5) dose held due to Gr 3 fatigue
061-1107	17 Jul 01 (C2W4) dose held due to Gr 3 skin rash
061-1110	04 Jun 01 (C1W3) dose held due to bilirubinemia, jaudice, urine abnormality, signs of progressive disease
061-1114	08 Jun 01 (C1W3) dose held due patient hospitalization
061-1120	06 Jul 01 (C1W4) dose held due to Gr 3 skin toxicity

Three patients received a total of four courses of C225 in the presence of grade 3 skin toxicity. As written, the protocol does permit this ("If a patient experiences a grade 3 skin toxicity, Cetuximab therapy *may* be delayed....").

Patient ID	No Dose Delay in the presence of grade 3 skin toxicity
061-1115	15 Jun 01 (C1W4) dose administered despite presence of Gr 3 acne-like rash
061-1117	02 Jul 01 (C1W4) and 09 Jul 01 (C1W5) doses administered despite presence of Gr 3 acne-like rash
061-1120	29 Jun 01 (C1W3) dose administered despite presence of Gr 3 skin toxicity

2.2.1.2.4 Discontinuations for Allergic Reaction to C225

Two patients experienced grade 3 allergic reaction during the test dose and were discontinued from the study.

Patient ID	Discontinuations for Allergic Reaction to C225
002-1148	10 Jul 01 (C1W1) Gr 3 allergic reaction during test dose, patient discontinued from study
002-1152	13 Jul 01 (C1W1) Gr 3 allergic reaction during test dose, patient discontinued from study

2.2.1.2.5 Dose Delay for Other Toxicities

Five patients had doses of C225 held for reasons other than grade 3 skin toxicity or intercurrent illness. In four of these cases, the dose was held at the patient's request or because the patient did not come to the clinic for the scheduled appointment. In the fifth case, no reason was provided.

Patient ID	Dose modification / Deviation
002-1144	30 Jul 01 (C1W4) dose not administered due to patient request to hold treatment (skin toxicity had resolved to Gr 2)
061-1107	26 Jul 01 (C2W5) dose held with no reason given (skin rash had resolved)
061-1120	10 Aug 01 (C2W2) dose not administered due to patient request for week off for vacation
061-1125	21 Aug 01 (C2W5) dose not administered due to patient request for week off for vacation
061-1141	13 Sep 01 (C2W5) dose not administered because patient did not come into clinic due to WTC disaster

According to the protocol, any occurrence of a grade 3 skin toxicity required that the patient be sent for a dermatological consultation and that photos be taken of the skin toxicity at the time of the grade 3 skin toxicity and when the toxicity resolved. Grade 3 skin toxicity was reported in nine patients. In seven of these patients, photos were not obtained at the time of the skin toxicity and/or upon resolution.

Patient ID	Dose modification / Deviation
001-1133	Follow-up photos not obtained per protocol at resolution of rash
001-1138	Photos not obtained per protocol at time of Gr 3 skin toxicity
001-1160	Photos not obtained per protocol at time of Gr 3 skin toxicity. Follow-up dermatology appointment cancelled by patient and was not rescheduled.

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061-1107	Photos not obtained per protocol at time of Gr 3 skin toxicity or at resolution of rash
061-1115	Dermatology consult with photos not obtained per protocol
061-1117	Photos not obtained per protocol at resolution of rash
061-1120	Photos not obtained per protocol at time of Gr 3 skin toxicity or at resolution of rash

2.2.1.3 Key Findings

Two patient did not meet eligibility criteria - one patient had progression 6.3 months and the other 10.6 months following last irinotecan.

The single most common protocol violation was administration of a C225 infusion late, typically 2 days late but in one case as much as one week late.

Several patients with ≥ grade 3 skin toxicity did not have photographs of the skin lesions taken.

2.2.1.4 DISCUSSION

There were few eligibility, dosing or dose modification violations identified in the BLA database. Of note, only relevant CRFs were reviewed - a small fraction of the total number of CRFs for which data are represented in the database. The accuracy of the database cannot be guaged from this review.

2.2.1.5 CONCLUSIONS

Of the protocol violations identified, none would be expected to invalidate the findings of the study. The number and type of protocol violations identified are consistent with those typically seen in a study of this type.

2.2.2 IMCL CP02-0141 Refractoriness to Irinotecan

2.2.2.1 Review of Final Study Report

2.2.2.1.1 Summary Of Evidence For Efficacy In Irinotecan-Refractory Patients For IMCL CP02-0141

The following summarizes data available within the BLA submitted to the FDA to substantiate the claim that patients enrolled to study IMCL CP02-0141 (Phase II Study of an Anti-Epidermal Growth Factor Receptor (EGFR) Antibody, Cetuximab, in Patients with Irinotecan-Refractory, Stage IV Colorectal Carcinoma).

2.2.2.2 METHODS

2.2.2.2.1 Data Reviewed

There are few data present in the BLA database upon which to judge whether a patient was refractory to irinotecan. Only two pages of the CRF collected relevant data. The following is a list of the 8 datapoints collected in the CRF which might help determine whether a patient had irinotecan-refractory disease at the time of enrollment into the study.

1. On the CRF page titled ENROLLMENT CRITERIA, under the heading INCLUSION CRITERIA: *ALL MUST BE CHECKED YES TO BE ELIGIBLE*, the question is asked:

- "Patient has documented progressive disease $\leq$ 6 months after receiving an irinotecan-containing regimen". Accepted answers are YES or NO.

2. On the CRF page titled PREVIOUS THERAPY FOR COLORECTAL CANCER, the following data are captured for each previous therapy:

- a box to record CHECK HERE IF PATIENT DID NOT RECEIVE ANY PREVIOUS THERAPY
- a box to record TYPE OF THERAPY code for each prior therapy
  - TYPE OF THERAPY codes are:
    1 = Chemotherapy,
    2 = Hormonal,
    3 = Immunotherapy,
    4 = Radiotherapy
- a SPECIFY blank to record a written comment specifying the type of each prior therapy
- a box to record a BEST RESPONSE code for each prior therapy
  - BEST RESPONSE codes are:
    1 = Complete Response,

2 = Partial Response,
3 = Progressing Disease,
4 = Stable Disease,
5 = Palliative,
6 = Adjuvant,
7 = Unknown

- a fill-in-the-blanks space to record DATE STARTED M/D/Y for each prior therapy
- a fill-in-the-blanks space to record DATE ENDED M/D/Y for each prior therapy

Patient data listings contained within the Clinical Study Report of the BLA were reviewed.

CRFs were **not** provided as part of the BLA database submitted by ImClone Systems Inc., with the exception of patients who were represented in an SAE or Death narrative. However, the CRFs were obtained from ImClone Systems Inc. for all patients as part of this review. CRFs for all responding patients were reviewed as part of this report.

2.2.2.3 RESULTS

2.2.2.3.1 Response Among Refractory Subgroups of Patients

Fifty-seven patients received C225 in the trial.

Fifty-six (56) of these 57 patients were listed as having a recorded "YES" answer to INCLUSION CRITERIA #2 (Patient has documented progressive disease ≤ 6 months after receiving an irinotecan-containing regimen). This suggests that clinical trial personnel at the clinical trial site believed that 56 of 57 patients had progressive disease at the time of entry into the trial. This datapoint does not, however, establish refractoriness to prior irinotecan-containing therapy, and this 56 patient subset will not be characterized further here.

The degree to which patients had cancer refractory to prior irinotecan can be roughly inferred by looking at subsets of pretreated patients who progressed on the last irinotecan therapy prior to C225 and who also received their first dose of C225 soon after their last dose of irinotecan.

Thirty-one (31) of the 57 C225-treated patients had "progressive disease" listed as best response to treatment with an irinotecan-containing regimen, administered as the last chemotherapy regimen prior to enrollment in the study.

Of these 31 patients, the median "months since the last irinotecan" was 1.9 months (range 0.5 to 6.3 months). In 27 of 31 patients, the "months since last irinotecan" was ≤ 3 months. In 16 of 31 patients, the "months since last irinotecan" was ≤ 2 months. In 11 of 31 patients, the "months since last irinotecan" was ≤ 1.5 months.

The number of patients with BMS objective tumor responses according to these inferred-refractory subsets are listed in the table below:

TABLE 10 PATIENTS WITH BMS OBJECTIVE TUMOR RESPONSES ACCORDING TO PATIENT SUBSETS

CRF response to most recent irinotecan	Duration since the most recent irinotecan (months)	Number of patients in subgroup	Number of responses in subgroup (%) [95% CI]
any	any	57	6 (10.5) [4.0-21.5]
PD	any	31	4 (12.9) [3.6-29.8]
PD	≤ 3 months	27	3 (11.1) [2.4-29.2]
PD	≤ 2 months	16	2 (12.5) [1.6-38.4]
PD	≤ 1.5 months	11	2 (18.2) [2.3-51.8]

2.2.2.3.2 Evidence for Objective Tumor Response

Six (6) patients of 57 C225-treated patients are listed in the BLA as having an objective tumor response. The CRFs for these six responding patients are available for BMS review. Using the protocol definition of PR and assuming that single lesion progression is judged by comparisons to *baseline* and not to nadir, all 6 patients do meet the literal criteria for a partial response according to listed tumor measurements.

The assumption of comparison to baseline is a clinically reasonable assumption. However, values of a derived variable within the BLA (single-lesion tumor responses by course) contradict this assumption, suggesting that for two of six responding patients, the overall best response to C225 was stable disease. A detailed explanation of this issue is provided in Appendix 1.

The BLA data for all six responding patients are critically reviewed in detail below.

2.2.2.3.3 Evidence for Irinotecan-refractory Disease Among Responding Patients

In the following table, relevant data for the six patients with a partial response are listed:

Patient ID	Last Regimen	Duration of last irinotecan	Best response to last irinotecan	Months from last irinotecan to first C225
061-1108	CPT-11, 5-FU, LCV	~5 months	PD	0.7
002-1151	CPT-11, 5-FU, LCV	~4 weeks	PD	1.2
002-1150	CPT-11, 5-FU, LCV	~3 months	SD	2.2

003-1154	IRINOTECAN	~8 months	PD	2.6
001-1135	IRINOTECAN	~3 weeks	PD	4.6
001-1128	IRINOTECAN	~11 months	SD	5.6

Two responders were listed as having progressive disease as best response to last irinotecan and receiving the first dose of C225 within 6 weeks of the last dose of irinotecan.

2.2.2.3.4 Review In Detail Of All Six Responders

The efficacy data for all six responders, in numerical order, are listed below.

Patient 001-1128, enrolled at DFCI, was a 57 year old white male diagnosed on 04JAN96 with a T2 N0 MX moderately differentiated carcinoma of the rectum. His prior anticancer therapy is listed as follows:

Type of therapy	Site/agent	Start Date	Stop Date	Best Response
Anticancer surgery	RECTOSIGMOID RESECTION	04JAN96	..	
Radiation therapy	RADIATION	-- JUL98	-- AUG98	Unknown
Other regimen	5FU/ LEUCOVORIN	-- AUG98	-- MAR00	Stable disease
Irinotecan regimen	IRINOTECAN	-- MAR00	-- JAN01	Stable disease

He is listed as having an ECOG performance status of 0 at baseline, EGFR 1+ tumor, and received first dose of C225 5.6 months after the stop date of CPT11. His sites of disease are listed as abdomen and liver at baseline. His measured sites of disease are listed as 2 liver tumors and 1 adrenal tumor ranging in size from 2.8 t0 8.2 cm in longest diameter at baseline. His measured sites of disease decreased in aggregate from SOP of 104.9 to 50.7 at the end of cycle 2. The measurements provided are consistent with a confirmed Partial Response by protocol definition, with the important technical caveat that this statement assumes that single lesion progression is determined by comparison to baseline.

Patient 001-1135, enrolled at DFCI, was a 38 year old Asian male diagnosed on 16SEP97 with a T3 N1 M0 moderately differentiated colon carcinoma. His prior anticancer therapy is listed as follows:

Type of therapy	Site/agent	Start Date	Stop Date	Best Response
Anticancer surgery	PARTIAL LEFT COLECTOMY	16SEP97	..	
Other regimen	5- FU, LEUCOVORIN	21NOV97	-- MAY98	Stable disease
Anticancer surgery	REDO OF LEFT COLECTOMY	15JAN99	..	
Radiation therapy	RADIATION 5040 GY	-- MAR99	-- APR99	Unknown
Anticancer surgery	REDO LEFT COLECTOMY REDO LEFT NEPHRECTOMY	08FEB00	..	
Anticancer surgery	PELVIC OMENTOPLASTY COLOSTOMY, PARTIAL EXCISION OF LEFT ABD. WALL	08FEB00	..	
Other regimen	5- FU	-- AUG00	-- DEC00	Unknown
Irinotecan regimen	CPT- 11	18JAN01	08FEB01	Prog. disease
Anticancer surgery	ENTEROENTEROSTOMY EXPLORATORY LAPAROTOMY, LYSIS OF ADHESIONS	21MAR01	..	
Radiation therapy	RADIATION 30 GY	03MAY01	21MAY01	Adjuvant

He is listed as having an ECOG performance status of 2 at baseline, EGFR 1+ tumor, and received first dose of C225 4.6 months from the stop date of CPT11. His sites of disease are listed as abdomen, liver and soft tissue at baseline. The site of radiation therapy is not specifically noted. His measured sites of disease are listed as 6 tumors of the liver and abdomen ranging in size from 2.3 to 7.5 cm in longest diameter at baseline. His measured sites of disease decreased in aggregate from SOP of 107.1 to 44 4 at the end of cycle 2. The measurements provided are consistent with a confirmed Partial Response by protocol definition, with the important technical caveat that this statement assumes that single lesion progression is determined by comparison to baseline.

Patient 002-1150, enrolled at FCCC, was a 49 year old white female diagnosed on 02JAN01 with a T3 N1 M1, EGFR 2+, moderately differentiated colon carcinoma metastatic to liver and lung at diagnosis. Her prior anticancer therapy is listed as follows:

Type of therapy	Site/agent	Start Date	Stop Date	Best Response
Anticancer surgery	SIGMOID COLECTOMY	10JAN01	..	
Irinotecan regimen	CPT- 11, 5 FU, LEUCOVORIN	26JAN01	04MAY01	Stable disease

She is listed as having an ECOG performance status of 2 at baseline and received first dose of C225 2.2 months following stop date of CPT11. Her sites of disease are listed as 4 lesions - 2 lung metastases and 2 liver metastases ranging from 2.0 to 4.2 cm in longest diameter at baseline. Her measured sites of disease decreased in aggregate from SOP of 34.0 to 11.7 cm2 at end of cycle 3. The measurements provided are consistent with a confirmed Partial Response by protocol definition.

Patient 002-1151, enrolled at FCCC, was a 65 year old white male diagnosed on 14MAR00 with T3 N1 M1 moderately differentiated colon cancer. His prior anticancer therapy is listed as follows:

Type of therapy	Site/agent	Start Date	Stop Date	Best Response
Anticancer surgery	RECTOSIGMOID RESECTION	14MAR00	..	
Other regimen	TEGAFUR AND LEUCOVORIN	27MAR00	23AUG00	Stable disease
Irinotecan regimen	CPT- 11	06OCT00	20APR01	Stable disease
Irinotecan regimen	CPT- 11, 5 FU, LEUCOVORIN	04MAY01	04JUN01	Progr. Disease

He is listed as having an ECOG performance status 0, EGFR 2+ tumor, and receive a first dose of C225 0.7 months after the stop date of CPT11. His measured sites of disease are listed as three separate liver lesions which decreased in aggregate from a sum of products (SOP) of 40.3 cm^2 at baseline to 7.4 cm^2 in cycle 3. The measurements provided are consistent with a confirmed Partial Response by protocol definition.

Patient 003-1154, enrolled at Indiana Cancer Pavilion, was a 70 year old white female diagnosed on 11MAY00 with a T3 N2 MX moderately differentiated colon carcinoma. Her prior anticancer therapy is listed as follows:

Type of therapy	Site/agent	Start Date	Stop Date	Best Response
Anticancer surgery	ANTERIOR COLON RESECTION WITH CHOLECYSTECTOMY	!MAY00	..	
Other regimen	5 FU/ LEUCOVORIN	06JUN00	26SEP00	Prog. disease

Irinotecan regimen	CPT- 11	10OCT00	24APR01	Prog. disease

She is listed as having an ECOG performance status of 0, EGFR 3+ tumor, and received first dose of C225 2.6 months from the stop date of CPT11. Her measured sites of disease are listed as 3 liver lesions ranging from 1.5 to 2.0 cm in longest diameter at baseline. Her measured sites of disease decreased in aggregate from SOP of 12.2 to 0.2 cm2 at end cycle 2. The measurements provided are consistent with a confirmed Partial Response by protocol definition.

Patient 061-1108, enrolled at MSKCC, was a 39 year old Asian male diagnosed on 01MAR00 with T3 N2 M0 moderately differentiated colon cancer. His prior anticancer therapy is listed as follows:

Type of therapy	Site/agent	Start Date	Stop Date	Best Response
Other regimen	INTRAPERITONEAL FUDR	- - -	- - -	Unknown
Other regimen	5FU/ LEUCOVORIN	- - -	- - -	Unknown
Anticancer surgery	RIGHT HEMICOLECTOMY	30AUG99	. .	
Anticancer surgery	LIVER RESECTION- SEGMENTS THREE AND FIVE WEDGE RESECTIONS	01MAR00	. .	
Anticancer surgery	GALL BLADDER RESECTION	01MAR00	. .	
Anticancer surgery	CHOLECYSTECTOMY	01MAR00	. .	
Irinotecan regimen	FLOXURIDINE/ CPT- 11	29MAR00	23AUG00	Comp. Resp.
Irinotecan regimen	CPT- 11	30AUG00	15NOV00	Stable disease
Irinotecan regimen	5FU/ LEUCOVORIN/ CPT- 11	29NOV00	25APR01	Prog dis.

He is listed as having an ECOG performance status of 0, EGFR 2+ tumor, and received a first dose of C225 1.2 months after the stop date of CPT11. His site of disease is listed as lymph node at baseline. His measured sites of disease are listed as a single "panaortic lymph node" which decreased from a baseline size of 1.8 x 1.9 cm to a size of 1.0 x 1.1 cm on measurements in cycle 2 and 3. Strictly speaking, the measurements provided are consistent with a confirmed Partial Response by protocol definition. However, there are no data to document that the "panaortic lymph node" contains metastatic tumor. Also of note, the patient received nearly five months of 5FU/ LEUCOVORIN/ CPT- 11 and yet is listed as having a best response of progressive disease to this therapy. This seems to be logically inconsistent and is unexplained by the listings.

2.2.2.3.5 Additional findings upon review of Case Report Forms (CRFs) provided on 4JAN02 by ImClone Systems Inc.

The CRFs provided are incomplete for an uncertain number of patients. For some patient records, tumor measurement, adverse event, and CRF correction pages appear to be missing from the record provided.

Of the CRF pages provided, unexplained discrepancies between the BLA database and the CRFs are apparent. The extent of these discrepancies will be quantitated by audit of the databases. For responding patients, none of the CRF data contradicted the conclusion that they experienced a best overall response of partial remission.

2.2.2.3.6 Key Findings

- **Nothing in the inclusion criteria of the protocol required that patients eligible for enrollment have irinotecan refractory disease.** Inclusion criteria #2 did require that a patient have documented progressive disease ≤ 6 months after receiving an irinotecan-containing regimen, however this does not insure that a patient has irinotecan-refractory disease. For example, a patient with irinotecan-sensitive disease who was taken off irinotecan and then progressed within ≤ 6 months would be eligible for enrollment.

- There are few datapoints collected on the CRF and reported in the BLA which might help determine whether patients on IMC CP02-0141 had irinotecan-refractory disease.

- **The data collected in this trial are insufficient to determine irinotecan refractoriness for any patient.**

- However, of the data collected, **irinotecan refractoriness can be inferred for 11 of the 57 patients** enrolled as follows. Eleven (11) patients out of 57 total *had a best response* to last irinotecan of progressive disease *and* were treated with C225 within 6 weeks of stop date for that irinotecan.

- Of these 11 inferred-refractory patients, 2 patients (#1108 and 1151) had a partial response. The data supporting PR are compelling for patient 1151, but not for 1108, as noted below.

- The data that are listed in the database regarding best response to prior therapy contain logical inconsistencies. It appears that "final response to therapy" was often recorded rather than "best response to therapy".

- **In my opinion, there are five patients (#1128, 1135, 1150, 1151 and 1154) enrolled at three separate institutions, whose data compellingly support a determination of partial response to single agent C225.** One patient (1108) at MSKCC had a single, relatively small lymph node as the basis of tumor measurement; this patient's data for PR are not compelling in my opinion.

- For two patients (#1128 and 1135), confirmation of a partial response requires a technical assumption that single lesion progression is determined by comparison to baseline. The BLA database for response assessment contains discrepancies between the recorded single-lesion response assessment and this assumption, and there are additional discrepancies in the BLA database between the recorded single-lesion response assessment and the overall response by course.

- No SAEs were reported for the 6 responding patients.

- **Thirteen (13) patients are listed as having an overall best response of stable disease.** The CR+PR+SD rate is 19/57 patients, or 33.3% (95% CI, 21.4 to 47.1).

- All data in the BLA are censored at 12 October 2001. Therefore, the median duration of response has not been reached, and **no conclusions can be drawn regarding durability of response from data in the BLA.** As of 12OCT01, all responding patients remained on study without recorded progression of disease for durations ranging from 78 to 161 days.

- For responding patients, **other possible indicators of clinical benefit** were reviewed including performance status, increases in weight, clinical comment (eg, to find lessening pain or improving bowel habit abnormalities).
  - Five (5) of 6 responders had weight gain between 1-3 kg; 1 patient lost 1 kg.
  - None of the clinical comments document additional benefit among the responders.
  - Serial ECOG performance status values were not collected. ECOG PS was recorded only once (on the pre-treatment CRF). Changes in performance status cannot therefore be determined for any patient.
  - No Quality of Life data were collected.

- Early onset (study day ≤ 15) grade 1-2 acneiform rash occurred in all responders except one (#1135).

2.2.2.3.7 Conclusions Regarding Efficacy

The BLA database for IMCL CP02-0141 does not contain data to determine irinotecan refractoriness for any patient. Collection of these data would likely require collection of source documents from *referring* centers. Many or most of these documents are probably *not* contained at the enrollment centers for this trial. Collection of these source documents for independent review or to provide the needed source data verification required of collection of new datapoints by additional CRF completion would require significant resources and time. If it becomes necessary to determine whether study subjects had 5FU refractory tumor, additional source documentation collection and resources would be required.

In my opinion, base upon available recorded data in the BLA, there were 5 patients (out of 57 patients treated) who experienced a convincing objective tumor response while receiving single agent C225. Based on this, I believe C225 has anti-tumor activity against metastatic colorectal carcinoma.

Although C225 is active, the magnitude of clinical benefit for patients whose tumors shrink from single agent C225 is unclear. Follow-up is too short in the BLA database to determine duration of response. Weight gain among responders hints at clinical benefit beyond tumor shrinkage, however performance status and QOL were not measured, and clinical comments do not document additional clinical benefit.

2.2.3 IMCL CP02-0141 Safety

2.2.3.1 Study 0141 Patient Deaths

Data regarding patient death can be obtained from the REPORT OF PATIENT DEATH (page 120) and SURVIVAL FOLLOW-UP (page 122) CRF pages.

1. The following are captured on the REPORT OF PATIENT DEATH CRF page:
- the question DID PATIENT DIE WITHIN 30 DAYS OF DISCONTINUATION OF THERAPY?, with an option to check a box marked YES or NO
- for a YES answer, the DATE OF PATIENT DEATH is to be provided in a M/D/Y format in space provided
- the question WHAT WAS THE PRIMARY CAUSE OF DEATH?, with options to check one box only for DISEASE PROGRESSION, DISEASE-RELATED COMPLICATION, INTERCURRENT OR UNRELATED ILLNESS/EVENT, EVENTS RELATED TO CETUXIMAB, EVENTS RELATED TO CHEMOTHERAPY, or UNKNOWN

2. The following are captured on the relevant portion of the SURVIVAL FOLLOW-UP CRF page:
- PATIENT STATUS AS OF (date) is to be provided in a M/D/Y format in space provided, with option to check a box for ALIVE, DEAD (with date of death to be provided in a M/D/Y format in space provided), or LOST TO FOLLOW-UP

Based on review of the "Patient Deaths with 30 Days of Last Infusion" data listing, four patients were identified as having died within 30 days of the last cetuximab infusion in the 0141 study. Of these, two patients were stated to have died of disease progression (002-1123 and 061-1110), one patient was stated to have died of a disease-related complication (001-1138, pulmonary embolism), and one patient was stated to have died of intercurrent illness (002-1156, respiratory insufficiency and septic shock). Patient narratives were not included in the BLA for any patient.

Review of the SURVIVAL FOLLOW-UP CRF page did not reveal any additional patients as having died within 30 days of the last cetuximab infusion.

2.2.3.2 Study 0141 Hospitalizations

Data on hospitalizations can only be discerned from the ADVERSE EVENTS (page 100) CRF page. For a given adverse event, under ACTION TAKEN, there is an option for NEW OR PROLONGED HOSPITALIZATION. No other fields are available to record the details of the hospitalization.

A total of 13 patients were identified who had at least one episode of hospitalization not specifically required by the protocol. From the data available, it is possible to identify the reason for hospitalization, the number of hospitalizations per patient, but not the duration of hospitalization. Patient narratives were not included in the BLA for hospitalizations. The FDA has requested narratives for these hospitalizations. The data in the BLA are insufficient to provide clinically meaningful narratives. Data on duration of hospitalization must be collected, entered and analyzed per FDA request.

2.2.3.3 Study 0141 Discontinuations: inconsistencies and discrepancies that impact on the interpretation of the toxicity profile

Preliminary review of the data listings, CRFs, and reports indicate that are inconsistencies and/or omissions that may impact the assessment of the toxicity profile. For example, patient 001-1134 is listed in the database as "withdrew consent" as the reason for discontinuation from the study. The CRF for this patient was not provided with the 0141 CRFs, so no assessment can be made with regard to the patient's adverse events during the treatment course and at the time the patient withdrew consent.

In summary, narratives for all patient deaths and discontinuations will be required. Preliminary review of the SAE reports recently received from ImClone appear to be sufficient to evaluate the cases in detail for the purpose of writing the narratives. However, additional information may be required once the review is undertaken. Additional data collection will be required to complete narratives for all hospitalizations, if requested by FDA.

2.2.4 IMCL CP02-0141 Data Entry Review

2.2.4.1 Audit Summary for IMCL CP02-0141

A CRF (including query forms) versus database audit was conducted by BMS Data Management on Jan 9, 2002. For the 60 patients for which CRFs were provided, Level 1 variables were checked. For the 12 randomly selected patients, Level 2 variables were checked. The randomly selected patients and the variables selected for auditing were determined by the BMS statistician. Listings were generated by BMS statistical and programming staff and were based on the raw database values. The two levels are as follows:

Level 1 – Critical Variables (56 patients)	Tumor Measurements (all lesions - all courses including baseline) Measurement Date, Lesion Site Text, Measurable/ Evaluable Indicator, First Measurement, and Second Measurement
Level 2 – Important Variables (12 patients)	Adverse Event (all adverse events) AE Text, Onset Month, Onset Day, Onset Year, Resolution Month, Resolution Day, Resolution Year, Toxicity Grade, and SAE indicator Cetuximab Administration - Test Dose Dosing Month, Dosing Day, Dosing Year, Total Test Dose, Dose Level, and Total Load Dose Cetuximab Administration Dosing Month, Dosing Day, Dosing Year, Dose Level, and Dose Administered Discontinuation Discontinuation Reason Report of Patient Death Death Within 30 Days question, Death Month, Death Day, Death Year, and Cause Prior Therapy Therapy Text, Best Response, Start Month, Start Day, Start Year, Stop Month, Stop Day, Stop Year

2.2.4.2 Findings:

Denominators were estimated based on the average number of datapoints for the variables for the patients being audited. Any datapoint which was different from the documentation found in the CRFs provided was counted as an error. Please note that this includes datapoints in the database for which no CRF page could be found.

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TABLE 11 FINDINGS

	Total Errors/Estimated Total Datapoints	Error Rate
Level 1 - Tumor Meas.	60 /2820	2.13%
Level 2 - Adverse Event	41 /864	0.46%
- Test Dose 0 /72	0.00%	
- Dosing	20 /540	3.70%
-Discontinuation	0 /60	0.00%
-Death	0 /300	0.00%
-Prior Therapy	1 /276	0.36%

Note: Acceptable error rates for BMS studies managed by BMS Data Management are 0.0% error rate for Level 1 variables and less than 0.5% for Level 2 variables.

2.2.4.3 Comments:

Randomly selected patients for the Level 2 audit were: 001-1128, 002-1144, 002-1156, 002-1159, 003-1158, 061-1105, 061-1106, 061-1113, 061-1115, 061-1120, 061-1125, and 061-1142.

No CRF was provided for 001-1134 although a tumor measurement listing was available.

The CRF for 001-1149 was provided, but the tumor measurement listing referred to the site as 002.

Documentation of these discrepancies will be kept in the Data Management Study folder for this study.

2.3 PLAN TO COLLECT ADDITIONAL DATA AND COMPARATOR SCANS

2.4 BMS REVIEW OF ERBITUX BLA CLINICAL PHARMACOLOGY DATA

The following is a summary of the review of the Erbitux clinical pharmacology data that has been summarized within the current BLA by ImClone Systems Inc. During the conduct of this pharmacology review several deficiencies became apparent that would likely be apparent to the FDA and thus be cited in any response. These deficiencies can be grouped as

1) bioanalytical issues;
2) pharmacokinetic analyses and subsequent interpretation, especially as it relates to dose selection; and,
3) general formatting of BLA data submission.

Each issue is addressed individually below. Although these issues were identified within BMS prior to the RTF letter, it was the opinion that these pharmacology deficiencies were likely to be manageable with a "clean" clinical dataset in this initial refractory setting. It was anticipated that considerable post approval pharmacology work would be requested by the FDA especially in support of subsequent first-line indications. In addition, it was anticipated that the submitted PK data could support labeling for this refractory colorectal cancer indication. Prior to the RTF no specific comments on the human biopharmaceutics data have been provided to ImClone Systems Inc.

2.4.1 Bioanalytical Methods (Serum Cetuximab And Anti-C225 Antibody Concentrations)

A thorough review of the bioanalytical methods for determination of serum Cetuximab concentrations as provided within the BLA was completed by Russell Weiner from Clinical Discovery. In addition, an initial review of the human anti-chimeric antibody assay (HACA) was also completed, however the limited documentation available prevented a thorough review. In addition, Daryl Sonnichsen and Russell Weiner visited ImClone Systems Inc. facilities on Dec 4, 2001 to meet with Dr. Floyd Fox, the individual responsible for the pharmacology data at ImClone Systems Inc. Importantly Dr. Fox is their head of Clinical Serology and has limited expertise with the interpretation of clinical pharmacology data.

Concerns were raised regarding the acceptability of the analytical data as it was obtained using instrumentation and software (Biacore) that are not 21 CFR Part 11 compliant. Specifically, data analysis is completed within a very open system involving at least 60 steps including multiple cutting and pasting steps. This open system would be in violation of 21 CFR part 11 without appropriate safeguards and validation. A 21 CFR Part 11 remediation plan will need to be put in place to address any FDA concerns. Other concerns regarding the ImClone Systems Inc. procedures/documentation for Cetuximab bioanalysis include: standard curve acceptance criteria, definition of the standard curve range, definition of lower limit of quantitation, insufficient number of quality control

(QC) samples (only two levels run where FDA requires a minimum of 3 in duplicate), acceptability of QC matrix, documentation of assay accuracy and precision and documentation of patient sample stability under storage and assay conditions.

The human anti-chimeric antibody assay (HACA) was not completed at ImClone Systems Inc., rather contracted out to labs at the University of Alabama. There is inadequate description and documentation of the HACA assay completed at UAB within the BLA. Criteria for a positive HACA response were that post treatment values must be >2x pretreatment baseline and value must also be greater than the values obtained from the normal population. The later of the two criteria is questionable because there are numerous examples in the normal population of individuals with unexplained reactivity to antibody therapeutics. The variability of the normal population should have no bearing on whether a patient post treatment produces anti-C225 reactivity. Determining if a patient has a positive antibody response should be based solely on the comparison of the patient's pre-treatment (baseline) versus post treatment values. The current methods for documenting an anti-C225 response could represent an underestimating HACA response determined using more traditional criteria.

During the meeting at ImClone Systems Inc., the above issues identified during the review of the BLA documentation were discussed with Dr. Fox. Although some of the issues appeared to be addressable with data already available at ImClone Systems Inc. or by experiments that could be readily conducted by ImClone Systems Inc. Although not critical, these issues raise potential concerns for regulatory reviewers and therefore should be considered as a liability of the current pharmacology dataset. Therefore, a 21 CFR Part 11 remediation plan document for the ImClone Systems Inc. Biocore assay system should be develop by ImClone Systems Inc.

2.4.2 Rationale For Dose Selection Summarized Within BLA

At the time that ImClone Systems Inc. initiated clinical development of Erbitux, to goal was to administer doses of the antibody that would be safe and would maintain serum Cetuximab concentrations greater than those needed to saturate the binding of tumor-associated EGFR in preclinical murine models. Based on preclinical work by Mendelson at al, this target concentration was reported to be 20 nM.

As early clinical development proceeded ImClone Systems Inc. changed the criteria for dose selection based on a new hypothesis that non-tumor associated EGFR binding in patients (especially liver and skin) might represent a large sink for Cetuximab which could limit availability of the antibody to tumor associated receptors. An extension of this hypothesis is that non-tumor binding of Cetuximab and subsequent receptor internalization represented a major route of elimination for Cetuximab that would theoretically become saturated. Thus at some point, systemic clearance of Cetuximab may become saturated which might be detected by estimation of patient serum pharmacokinetic parameters (total body clearance and half-life). Moreover, because Cetuximab does not bind to murine EGFR, this theoretical sink was not in-place during preclinical efficacy experiments. Therefore, effective exposures determined in preclinical

murine models might represent an underestimation of effective exposures required in patients. Thus, the target criteria for dose selection was changed by ImClone Systems Inc. to identify a dose at which systemic clearance (as determined by serum PK) became saturated.

As later described, ImClone Systems Inc.s evaluation of the patient PK data across multiple different dose escalations studies (monotherapy and combination studies) suggested that Cetuximab clearance decreased with increasing dose and it appeared to plateau (saturate) at dose of greater than 200 mg/m^2. Moreover, serum half-life appeared to increase with increasing dose and plateau at doses ≥ 300 mg/m^2 (a BMS critique of the PK analyses and interpretation follows). Based on all of the above and clinical toxicity data at doses of 500 mg/m^2, ImClone Systems Inc. selected the phase II regimen to be an initial loading dose of 400 mg/m^2 followed by repetitive weekly doses of 250 mg/m^2. With this regimen, ImClone Systems Inc. suggested that EGFR occupancy and pharmacologic activity would be sustained.

In addition, two ImClone Systems Inc. clinical studies were designed to specifically evaluate the effect of Cetuximab at the EGFR level, studies 9608 and 9709. In study 9608, patients with head and neck cancer received Cetuximab in combination with cisplatin. There were three cohorts based on the Cetuximab loading dose/weekly maintenance dose; 1) 100/100, 2) 400/250 and 3) 500/250 mg/m^2. Tumor biopsy specimens were obtained at baseline, 24-hours after the loading dose and 24 hours prior to the 3rd dose of Cetuximab. Biopsy specimens were evaluated for EGFR binding of Cetuximab by immunohistochemistry, EGFR kinase activity and EGFR/Cetuximab complex formation. A total of 12 patients were enrolled onto this study however, only 9 patients had samples that were assayed for some or all of these PD endpoints. Overall, the limited number of patients and fewer number of evaluable data across all the three PD assays prevented any truly useful information from being derived form this study. Cetuximab binding to EGFR was observed at all dose levels however, clear dose responses could not be discerned. In the 3 patients with evaluable data on residual EGFR kinase activity, inhibition by Cetuximab was reported but these data are too limited to be informative. Similarly EGFR/Cetuximab complex formation was reported, however, the variability of these few evaluable patients made the data uninterpretable. In the case of study 9709, only 4 patients were enrolled onto two treatment cohorts (Cetuximab loading/weekly maintenance doses of 200/200 and 400/250 mg/m^2. In only two patients, one for each treatment cohort were pharmacology samples obtained. Because of the limited participation on this study, the samples were never assayed and therefore this study provided no useful information.

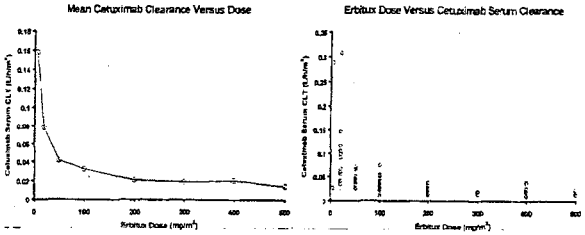
Although ImClone Systems Inc. repeatedly conveyed the above rationale for Cetuximab dose selection to investigators and regulatory agencies, it is important to note that the FDA was never convinced with this logic. On repeated occasions that ImClone Systems Inc. had dialog with the FDA, the agency requested PK data that would substantiate these dose selection claims. The requested supportive PK were only provided at the time the BLA was submitted. Of note, beyond the dose selection issue raised within the RTF

letter, detailed comments of the pharmacology data submitted within the BLA from the FDA pharmacology reviewer have not been received.

Serum Cetuximab concentration data, either detailed serum concentration versus time profiles or peak and trough determinations, were obtained for most of the patients treated on the majority of the clinical studies submitted within the BLA. For the early dose escalation studies of Cetuximab serum concentration profiles were obtained for individual patients to allow estimation of key PK parameters (half-life, clearance, volume of distribution). In the first-in-human study (9301) the range of Cetuximab doses evaluated was limited to between 5 and 100 mg/m^2. At these lower Cetuximab doses, relatively few patients are evaluable for pharmacokinetics per dose level and resulting serum Cetuximab concentrations were relatively low and remained measurable for a only short periods (1-2 days). Within study 9301 estimates of Cetuximab half-life of 24 hours or less were reported. However, these estimates of half-life may not be representative of the actual half-life because of the duration of measurable serum concentrations was limited by dose and assay sensitivity. Evaluation of the serum pharmacokinetics of Cetuximab at doses greater than 100 mg/m^2 was performed in later monotherapy or combination studies. Importantly, study 9301 is the only Cetuximab study for which the duration of PK sampling was extended beyond one week (28-days). All subsequent studies administered Cetuximab every week, and therefore the duration of PK sampling beyond the first dose for this chimeric IgG monoclonal antibody at current clinical doses (>100 mg/m^2) was restricted to 7-days. This is relevant because at the proposed labeled dose the median [range] terminal half-life of Cetuximab was estimated to be 3.5 days [1.7 to 14 days]. Because the a 7-day sampling period is of short duration relative to the estimated terminal elimination half-life, systemic clearance and volume of distribution estimates may be unreliable. This is likely to be especially true at doses of ≤ 50 mg/m^2. In view of the above limitation, the PK estimates from doses of ≤ 50 mg/m^2 are of questionable reliance and thus needed to be interpreted with great caution.

As described previously, linearity of PK was the predominant determinant for dose selection for Cetuximab. It was the assessment of ImClone Systems Inc. that with increasing dose, "mean" estimates of clearance decreased supporting their theory of saturable EGFR binding. Importantly, ImClone Systems Inc. evaluated and presented the mean data that dose not adequately represent the variability within the actual patient dataset, especially at the lower dose range. Figure 1a plots the mean clearance versus dose data used to support dose selection whereas Figure 1b presents actual patient clearance versus Cetuximab dose.

Figure 1: Cetuximab Clearance Versus Dose: A) Mean Data B) Actual Patient Data



What can be seen is that there is a large variability in clearance estimates at the lower dose range that clearly influences the mean data presentation. However, based on the described limitations for the available PK estimates for Cetuximab, especially at the low range of doses evaluated (5, 20 and 50 mg/m^2), it is not clear whether decreases in clearance (and increase in half-life) are real or an artifact of PK evaluations at low doses. Moreover, because Cetuximab is a chimeric IgG1 antibody, it is likely that the predominant and rate limiting mechanism of clearance is via the reticuloendothelial system (RES) and not by EGFR binding/international. Thus it is questionable whether systemic clearance, as determined via serum PK, would be a reasonable surrogate of EGFR binding. Therefore, the only clear means of establishing true dose or concentrations response data in support of dose selection is to directly evaluate the effects of Cetuximab on the EGFR receptor in tumor tissue or an appropriate surrogate tissue (i.e., skin).

Although the PK data do not provide strong support for dose selection, there remains a considerable amount of PK data that does provide relevant information regarding the pharmacokinetic behavior of Cetuximab in the patient population intended for marketing and be supportive of labeling statements. In almost all studies, repeated peak and trough serum Cetuximab data are available to characterize the exposures of Cetuximab with repeated weekly dosing. These data support that weekly administration of Cetuximab provide continuous exposures of antibody without clinically significant accumulation. Moreover, there dose not appear to be a decrease in serum concentrations with repeated dosing over periods of a year. This finding suggests that clearance of Cetuximab does not increase with repeated dosing supporting that neutralizing antibodies to Cetuximab (anti-C225 Abs) are not being formed in patients with repeated Erbitux dosing.

3) General Formatting of BLA submission.

The ImClone Systems Inc. Erbitux BLA does not follow traditional structure in that it does not contain a completed Section 6. Wherein Section 6 is expected to be a stand alone description of all biopharmaceutics information on the product, this section in the current BLA is reduced to a summary of the bioanalytical methods. All clinical pharmacokinetic and pharmacology data for Erbitux normally presented within Section 6 are described within Section 8, principally as sections or appendices of final clinical study reports. Staff from ImClone Systems Inc. state that this deviation from normal procedure was at the request of the CBER pharmacology reviewer. It is possible that the CBER reviewer realized that the because the amount of clinical pharmacology data to be provided for Erbitux was limited that this was a simpler approach. Regardless, it would have been preferable for the BLA to have followed the traditional approach of providing a separate and complete section 6 human biopharmaceutics summary.

In addition, a raw pharmacokinetic data and supporting patient demographic data are to be provided to the agency in usable electronic formats. BMS received copies of the SAS data transfer files that were provided within the BLA. In working with these files it is not clear that the format provided would have been agreed upon by the FDA nor would it be acceptable to the agency. In general, the data base is poorly structured and contains many missing fields, without explanations for missing data. The data files would be difficult for any FDA Biopharm reviewer to work with, making it difficult for them to complete their independent PK analyses. As this would make the reviewer's job more difficult to perform it might result in a more complex review. However, to date no comments from the Biopharm reviewer regarding the written or electronic format of the data have been received by ImClone Systems Inc.

2.4.3 BMS Clinical Discovery Proposal for BLA Resubmission:

It is recommended that a stand alone, traditional Section 6 Human Biopharmaceutics Summary be developed for Cetuximab at the time of any resubmission. This resubmission document will act to fulfill the FDA request for an integrated dataset and analyses of the pharmacokinetic profile of Cetuximab. This will involve a complete restructuring of the existing raw PK database, reanalysis of the PK data and representation of the PK findings with appropriate interpretations. In addition, it is anticipated that the agency will require additional pharmacology data to support dose selection. Whether these additional data will be required at the time of or may follow the resubmission will have to be discussed with the FDA.

2.4.3.1 Clinical Phamacokinetic Reanalysis

Two paths will be taken to more completely characterize the clinical pharmacokinetic behavior of Cetuximab in cancer patients. The first will involve a complete reanalysis of the existing PK data within BMS and a resubmission of this integrated database. Two types of pharmacokinetic analyses, standard noncompartmental and population-based PK

analyses, will be performed by experienced pharmacokineticists within BMS using established and validated PK software. The resulting electronic database will also be structured into a more usable format for the purpose of facilitating FDA review. The non-compartmental analyses will attempt to recreate the findings from ImClone Systems Inc., however, the final interpretation of the PK results will likely change. Moreover, it is anticipated a BMS PK analysis of the existing dataset will not be supportive of the dose selection, rather will provide descriptive data regarding the PK behavior of Cetuximab in the target patient population. These PK analyses would be expected to provide essential labeling information for Cetuximab. The population based analysis will better address whether individual patient variability in the PK behavior of Cetuximab are explainable by various patient covariates (age, sex, baseline renal and/or hepatic function, etc). If reliable data on the extent of tumor burden and the expression level of EGFR are available for patients, these parameters could be evaluated as requested by the agency.

2.4.3.2 Additional Clinical PK studies.

In addition to the above reanalysis it is recommended that a new single agent dose escalation study be performed to characterize the PK of Cetuximab in patients with cancer. Three potential deficiencies of the current dose escalation monotherapy PK dataset would be addressed by this study. First, the PK data would be developed using a bioanalytical assay, ELISA-based and developed by BMS, which would be regulatory compliant. It is anticipated that documenting comparable serum Cetuximab concentration data with the BMS-ELISA and ImClone Systems Inc.-Biocore assay systems would add further support for the validity of the existing database. A second deficiency of the existing database is that at Cetuximab doses of > 100 mg/m^2, insufficient duration of PK sampling has been utilized to date. With half-lives of up to 14-days being reported in individual patients, the sampling duration of 7-days is inadequate for accurate estimation of terminal elimination phase (half-life) and subsequent calculation of clearance and volume of distribution. Since the recommended clinical dose is above 100 mg/m^2, this issue could be raised as a liability by the agency. The new study would ensure that an appropriate period of PK sampling (up to 3 weeks) was performed to ensure that half-life is adequately characterized. Lastly, this single new study would provide a clean PK dataset in a Western patient population to be used prospectively to compare similar data obtained in Japanese patients in support of bridging discussions with the Japanese regulatory agencies. This relatively small PK study (24-30 patients) would evaluate a range of doses at the time of first dosing (50, 100, 250, 400 & 500mg/m^2) followed by a appropriate period of PK sampling and subsequent doses of Cetuximab (250 mg/m^2) would be doses on a weekly basis with repeated PK and trough measurements. Importantly, this study could be rapidly implemented and provide additional PK data for any Erbitux resubmission. Importantly, it not anticipated that this serum PK study of Cetuximab alone will address the dose selection question for the reasons previously described.

2.4.3.3 Additional Clinical Dose Selection Study

The principle pharmacology deficiency identified within the RTF was the weak rationale for dose selection and the agency clearly stated that they did not concur with ImClone Systems Inc.'s conclusions. Moreover, the FDA specifically requested that tumor saturation data be provided for Cetuximab to support dose selection. In addition, the RTF requests information on how extent of tumor burden and tumor EGFR expression might influenced the pharmacology of Cetuximab and thus dose selection.

In anticipation of and in response to FDA concerns for the available Cetuximab dose response pharmacology data, proposals for studies to address dose selection have been discussed within the BMS ADED organization. Using expertise within the established signal transduction programs and information about what has been completed by competitor compounds, a proposal for a clinical study has been discussed which is described below. It is the general impression that to adequately address FDA concerns regarding Cetuximab interactions with EGFR, additional clinical pharmacology data at the level of EGFR (tumor and/or skin) are required. Therefore a single agent Cetuximab study in patients with tumors document to express EFGR (1+ or greater) and that are accessible to repeated biopsies (e.g., H&N, metastatic breast) is proposed. The first dose of Cetuximab would be administered as a two hour infusion in four or five dose cohorts of 6 patients each (50, 100, 250, 400 or 500 mg/m^2). The second dose of Erbitux (fixed at 250 mg/m^2 as 1-h infusion) and the start of maintenance dose period would be given three weeks later with each subsequent doses given on a weekly basis. Pharmacology samples would be at multiple time points surrounding the first dose in all patients. [Below for consideration]

PK:	Detailed serum sampling from baselines through Day 21
Skin Bx:	Baseline, end of infusion (Day 1), Day 8, Day 15, Day 21.
Tumor Bx:	Baseline, end of infusion (Day 1), Day 8

It is possible that if the study could document that skin is an acceptable surrogate tissue for evaluating effects on tumor EGFR, that the reliance on tumor sampling might be reduced in favor of skin biopsy data. This would require that we demonstrate similar magnitude of effects by Cetuximab on the EGFR receptor in skin and tumor tissue with matched samples. Biopsy specimens would be evaluated for the expression of EGFR, as well as Cetuximab binding of EGFR. Additional assay looking a downstream tyrosine kinase activity and MAPK and ERK activation. Parallel serum pharmacokinetic data will allow exploration of Cetuximab serum concentration effect relationships with the various PD endpoints.

APPENDIX 1 - Discrepancies in the BLA Database

Discrepancies in the BLA database between single-lesion response determination for a visit, overall response for a patient, and the protocol definition of a partial remission.

In summary, two patients each have a single lesion which has progressed by comparison to the lesion's nadir, but which has not progressed by comparison to the lesion's baseline. The protocol definition of PR does not stipulate which comparison is correct. By assuming that the baseline is the correct comparison (as Nozar has done in his analysis); they are true PRs. Unfortunately, however, Listing 10 in the 0141 final study report implies that the nadir is the correct comparison, and contradicts the conclusion that they are true PRs. The situation is best clarified by the specific example below.

The interpretation hinges on what is not stated in the protocol definition of PR:
"a decrease by at least 50% of the sum of the products of the largest perpendicular diameters of all of the measurable lesions; all evaluable lesions must remain stable or regress; no simultaneous increase > 25% in the size of any lesions or the appearance of any new lesions may occur; in patients with measurable and evaluable disease, a stable response in evaluable disease will not detract from a complete or partial response calculated on the basis of the measurable disease, but the overall response can only be a PR"

Unfortunately, the definition does not state whether the simultaneous increase > 25% is relative to baseline or relative to nadir.

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The following are quoted verbatim from the final study report of 0141, Appendix 15.2 Patient Data Listings, Listing 10 Malignant Lesion Assessment:

patient ID	study day	tumor	product of diameters (cm2)	Tumor Response#	Derived Response#
001-1128	-18	RIGHT ADRENAL MASS	5.88	-	-
	39	"	5.20	SD	SD
	81	"	7.13	-	PD
	125	"	6.67	PR	PD
001-1135	-6	SEGMENT 8 LIVER	20.80	-	-
	36	"	9.86	PR	PR
	78	"	7.92	PR	PR
	120	"	13.86	NR	PD

-- Individual tumor response as assessed by the investigator, or derived from tumor measurements.

For patient 001-1128, the study day 81 scan was the scan to confirm an overall PR (only a single of three lesions is listed here for clarity). For the RIGHT ADRENAL MASS, the product of diameters on day 81 had increased by > 25% compared to nadir (day 39), but not compared to baseline (day -18). However, in Listing 10, the "Derived Response" for the single lesion is PD, which suggests that the correct comparison is to nadir.

There are therefore two cases:

#1: The correct comparison is to baseline, the "Derived Response" is incorrect in Listing 10, and the patient is a true PR (i.e., Listing 11 is correct for this patient).

#2: The correct comparison is to nadir, the "Derived Response" is correct in Listing 10, and the patient is not a true PR (i.e., Listing 11 is incorrect).

Clearly, #1 is in our favor, however, in either case there is a discrepancy in the database provided in the BLA.

The story for patient 001-1135 is the same in concept: the single lesion has progressed by comparison to nadir and has not progressed by comparison to baseline. The protocol does not state which is the correct comparison. In either case, there is a discrepancy in the database.

So in summary, two patients each have a single lesion which has progressed by comparison to the same lesion's nadir, but which has not progressed by comparison to the lesion's baseline. The protocol definition of PR does not stipulate which comparison is correct. It seems to be in our best interest to compare single lesions to their baseline, and therefore to agree with Nozar that these patients meet the definition for PR. However, regardless of which comparison is correct, there is a discrepancy in the database provided

in the BLA, and this discrepancy may provide an FDA reviewer the basis to contest the overall partial response determination for two patients.

Mr. STEARNS. Thank you, Mr. Chairman.

Mr. GREENWOOD. The Chair thanks the witnesses for their patience, and calls our third and final panel, consisting of Dr. Patricia Keegan, Deputy Division Director, Center for Biologics Evaluation and Research at the Office of Therapeutic Research and Review, Division of Clinical Trials Design and Analysis, at the U.S. Food and Drug Administration; Dr. Richard Pazdur, Director of the Division of Oncology Drug Products, Office of Drug Evaluation, Center for Drug Evaluation and Research, at the FDA; Dr. Lee H. Pai-Scherf, M.D., Medical Officer, Clinical Reviewer, Center for Biologics Evaluation and Research, Office of Therapeutic Research and Review, Division of Clinical Trials Design and Analysis, Oncology Branch, FDA; Dr. George Mills, Acting Chief, Team Leader, Center for Biologics Evaluation and Research, Office of Therapeutic Research and Review, Division of Clinical Trials Design and Analysis, Oncology Branch, FDA; and Dr. Susan Jerian, M.D., Medical Officer, Team Leader, Center for Biologics Evaluation and Research, at FDA.

Thank you all for your presence, and I thank you all for your forbearance and patience. You are aware that this is an investigative hearing, and that it is the practice of this subcommittee when holding such hearings to take testimony under oath. Do any of you object to giving your testimony under oath?

[No response.]

Mr. GREENWOOD. You are also aware that you are entitled pursuant to the rules of the House and this committee to be represented by counsel. Do any of you wish to be represented by counsel?

Mr. PAZDUR. Yes. I have my personal lawyer, Stephen Lieberman.

Mr. GREENWOOD. Stephen Lieberman is with you?

Mr. PAZDUR. Yes.

Mr. GREENWOOD. Very well. Anyone else? Yes, Dr. Keegan?

Ms. KEEGAN. I am represented by the FDA General Counsel.

Mr. GREENWOOD. You are represented by the FDA General Counsel?

Ms. KEEGAN. Yes.

Mr. GREENWOOD. Dr. Jerian.

Ms. JERIAN. I am represented by the FDA General Counsel.

Mr. GREENWOOD. Okay. Anyone else?

Mr. MILLS. Dr. Mills, FDA General Counsel.

Mr. GREENWOOD. And could you name the General Counsel for us that is representing all of you?

Ms. KEEGAN. Michael Landa.

Mr. GREENWOOD. The Chair would note that each of you is here under subpoena. The Chair would also note that it what we call a friendly subpoena, and that we felt that it was important to issue to protect any legal concerns that might come from your rules and regulations with regard to confidentiality. Would you please all rise and raise your right hand.

[Witnesses sworn.]

Mr. GREENWOOD. Okay. Thank you. And you may be seated, and I understand that you have chosen not to have opening statements, but are here to respond to our questions, and we thank you for that.

TESTIMONY OF PATRICIA KEEGAN, DEPUTY DIVISION DIRECTOR, CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, OFFICE OF THERAPEUTICS RESEARCH AND REVIEW, DIVISION OF CLINICAL TRIAL DESIGN AND ANALYSIS, U.S. FOOD AND DRUG ADMINISTRATION; ACCOMPANIED BY RICHARD PAZDUR, DIRECTOR, DIVISION OF ONCOLOGY DRUG PRODUCTS, OFFICE OF DRUG EVALUATION I, CENTER FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD AND DRUG ADMINISTRATION; LEE H. PAI-SCHERF, MEDICAL OFFICER, CLINICAL REVIEWER, CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, OFFICE OF THERAPEUTICS RESEARCH AND REVIEW, DIVISION OF CLINICAL TRIAL DESIGN AND ANALYSIS, ONCOLOGY BRANCH, U.S. FOOD AND DRUG ADMINISTRATION; GEORGE Q. MILLS, ACTING CHIEF, TEAM LEADER, CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, OFFICE OF THERAPEUTICS RESEARCH AND REVIEW, DIVISION OF CLINICAL TRIAL DESIGN AND ANALYSIS, ONCOLOGY BRANCH, U.S. FOOD AND DRUG ADMINISTRATION; AND SUSAN M. JERIAN, MEDICAL OFFICER, TEAM LEADER, CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, DIVISION OF CLINICAL TRIAL DESIGN AND ANALYSIS, ONCOLOGY BRANCH, U.S. FOOD AND DRUG ADMINISTRATION

Mr. GREENWOOD. And let me begin——

Ms. KEEGAN. Mr. Chairman, we were wondering if you would be interested in having us present, or having myself present, some background on the FDA chronology of this application as it might streamline your questioning.

Mr. GREENWOOD. Sure. If you are prepared to do that, that would be most helpful, please. You are recognized.

Ms. KEEGAN. I am Dr. Patricia Keegan. I wanted to say that the application, the IND, for ImClone's Erbitux, was filed in 1994, and that the IND application was filed in order to conduct clinical studies in humans in the United States with the FDA.

A number of studies have been submitted to that IND, and in the late spring of 2000, ImClone contacted us to talk and to request that we have a meeting to talk about what they thought were some very promising results with a Phase II study that has been submitted to that IND, and the study conducted in 1999 as you have heard.

We agreed to meet and talk about the results of that study, and we met with the company in August of 2000. The discussion at that time was centered on whether or not the promising results that were being reported to us, which was a response rate of about 20 percent in patients with metastatic colorectal cancer, with no available therapy, might be sufficiently promising to warrant consideration for an accelerated approval based on that end point of that observation of tumor response or tumor shrinkage.

We discussed at that meeting the adequacy of the trial itself, and I would say that we concur with the statements made by Dr. Waksal that that trial was not intended either by ImClone or ourselves to be a registration or a major efficacy trial.

And the specific design elements of that trial had not been evaluated critically by the FDA. At the time of the meeting, we sat to discuss whether or not the data, which indeed appeared to be

promising based on the report, could be used, or some portion of the study results could be used.

Also, what the limitations of that data were and what additional information that the FDA might need to consider whether or not there might be enough data to submit an application.

The critical elements of that protocol that we looked at were that a significant proportion of the patients, close to 90 percent, were purported to have had tumor growth, progressive disease, while receiving irinotecan therapy.

We understood at the time that there was progressive disease in the face of at least two cycles of irinotecan therapy so that the patients had an adequate amount of drug in order to determine whether or not their tumor would shrink or would grow.

In addition, patients whose tumors had not shrunk on irinotecan that were enrolled in the study went on to receive not only Erbitux, but irinotecan at the same dose and schedule that they had received earlier.

These design elements were critical in our considerations because we felt that they were necessary to determine whether or not the results that were being observed might be attributed to Erbitux, the addition of Erbitux, or whether we could not discern that.

And it was on that basis that we felt that the design might be adequate to assess whether the addition of Erbitux was causing tumor shrinkage. We also recognized that the design was not adequate to identify other aspects that were important here.

And the other aspect was whether or not irinotecan was contributing to that effect. At the meeting, we discussed ImClone's perceptions of their drug and how they felt that it worked. Specifically, that Erbitux would not act alone, but would only act in collaboration with a chemotherapy drug such as irinotecan.

And in fact the way that Erbitux worked was to overcome the tumor resistance to that prior therapy, the irinotecan, in this case. And that was the way in which it was effective. We have asked where the data to support that statement might exist. And the response that we received was that it was based upon prior other studies conducted in human beings, and animal studies that were conducted.

And that that data resided currently in the application as of August 2000. Based on those discussions, we informed the company that we thought that there might be reasonable promise to go forward and pursue discussions of a license application.

Subsequent to that time, we conducted an extensive review of the information in the file, and we reached a different conclusion from that provided by ImClone, which was that we did not think that the information currently in the file showed that Erbitux would not be active by itself.

Our conclusion was that there was insufficient information to judge whether it would work alone or not, and that the only way to address that was to conduct an additional trial.

In January of 2001, we conveyed to the company, both by letter and in a subsequent telephone conversation, that we disagreed with their assessment of the data in the file, and that they needed to conduct another study.

The representatives of ImClone did in fact begin another study that was begun in April of 2001, and that study was considered critical to provide a critical piece of evidence for the license application that they were intending to file.

That is the study that I think some refer to as 0141. And in June of 2001, the initial portions of the license application were filed and submitted to the FDA, and the last portion of that application, which was the clinical study data, was submitted in October 2001 as you have heard.

And I think the rest is obvious to the committee that upon review of that information, we felt that there were multiple deficiencies in the application, primarily arising not only from the inconsistencies and defects in the data and missing data, but also issues with regards to the conduct of the clinical trial.

Mr. GREENWOOD. Thank you. Dr. Keegan, why don't I start my questioning with you, and I would ask anyone else if you feel that you can add to her response, please do, or maybe you feel it is more appropriate to respond.

According to an October 12, 2001 e-mail from BMS chief scientific officer Peter Ringros to other BMS executives, Bristol-Myers Squibb executives, which reads, "I just had Sam Waksal on the phone regarding the single agent data. Apparently, it came out at 13 percent, which he feels is half the C225, plus CPT-11, data. They have informed the FDA, who were pleased, and confirmed that they would be on for the February 28 ODAC," which is the Oncological Drug Advisory Committee.

"He reckons that they will be on the market by March. I am planning to meet with Sam in New York the week after next."

Did any of you ever get contacted by ImClone about the results of the study testing Erbitux alone before ImClone completed its application submission on October 31, 2001?

Ms. KEEGAN. I don't believe I can recall any contacts regarding that before the end of the submission.

Mr. GREENWOOD. Anyone else?

[No response.]

Mr. GREENWOOD. Okay. Did any of you ever inform anyone at ImClone that they would be on the agenda for a February 2002 ODAC meeting?

Ms. KEEGAN. I did not.

Mr. GREENWOOD. Anyone else?

[No response.]

Mr. GREENWOOD. Dr. Pazdur, the FDA announced as the protocol design of the ImClone 9923 is seriously flawed, not adequate, or well controlled. Are you familiar with the protocol design?

Mr. PAZDUR. That was the original protocol that had irinotecan, plus CPT-11, plus Erbitux, correct? The original study?

Mr. GREENWOOD. Yes.

Mr. PAZDUR. Yes, I believe—you are asking for my opinion regarding that trial?

Mr. GREENWOOD. Yes.

Mr. PAZDUR. I believe that trial was a flawed trial for a registration trial. It really never answered the question do you need irinotecan with Erbitux, and that is a critical question to be answered here.

The whole development of this drug, I think, was one of very—it put the drug in very serious regulatory jeopardy, and violated several principles of medical oncology.

First of all, a heavy reliance on pre-clinical activity and pre-clinical design is based on animals models. We know that animal models can give us an inclining or a suggestion of where to go.

But to conduct a whole development plan and a sole development plan on an animal model is a very risky venture. Second, they are asking patients to continue a drug, irinotecan, after they have progressed, or after their tumors have gotten larger on this.

This violates every principle that I know of in medical oncology, and in order to do that, you better have very good evidence that that is the thing to do here before you just go ahead and do it.

The drug, irinotecan, is a fairly toxic drug, and in the original registration trials for that drug, there were at least a 3 to 5 percent death, as well as a 20 percent hospitalization rate for toxicity related to irinotecan.

Again, if you are using this drug in a relatively unconventional study after the tumors have grown, it again points to the need to have adequate confirmation that this is a thing to do.

The way that this drug should have been developed is in a randomized trial. If they really believed that you needed the combination, they needed to do a randomized trial, which is being done now, looking at irinotecan, plus their drug, plus Erbitux alone. That would be the correct way of developing this drug.

Mr. GREENWOOD. Well, did the FDA share that information or make that suggestion to ImClone? Did you say to them—I mean——

Mr. PAZDUR. Could I say just one thing?

Mr. GREENWOOD. Please.

Mr. PAZDUR. I am not a member of the review team, and I am from a different center here, although my expertise is in colorectal cancer.

Mr. GREENWOOD. Okay. What Dr. Pazdur just said was pretty damming information. He said that this is a risky venture, and he said that if you really want to get this drug approved, you should have developed a randomized trial. That is language that even I can understand.

Did the FDA—do you agree with Dr. Pazdur, and if you do, is that a recommendation that the FDA shared with ImClone at any time in this long tortured history?

Ms. KEEGAN. What I would say is that the company believed based on data which we didn't find as compelling as they obviously did, that this drug would not be active on its own.

And if one truly believed that to embark on a large randomized controlled trial, might not be in the best interests of patients who got the Erbitux by itself, because one would enter it with the presumption that none of those patients would respond, and I think we would all find that to be a disturbing way to develop the drug if one was truly convinced by the data.

We did not find that data compelling, but we actually reviewed that data after the fact, after the Phase II study was completed. Based upon that, we recommended that a randomized study be performed. The company was persistent in their belief that Erbitux is

not going to be an active agent, or would not have been an active agent when give alone.

And they requested permission to conduct a small study in which the premise, the hypothesis, was that no patient would respond. And if they showed that in a relatively small number of patients, it could stop the exposure to patients of what they felt would be an ineffective therapy.

We recognized that could have been a risky approach because their premise could have been wrong, and in fact it turned out we believe to be wrong, although I would have to say we have not yet verified any of the data even in the single-agent study.

Mr. GREENWOOD. Given the limited time we have, I had two more questions of a very general nature. Where did this company go wrong? Where did ImClone make its gravest errors?

Because what strikes every one of us is that there is this enormous gap between the buzz on this drug. This is attracting capital by the hundreds of millions, and this was attracting a company with the prestige of Bristol-Myers Squibb, and they put $2 billion on the table.

This was a drug that was touted as the wonder drug or perhaps the best drug ever developed for cancer, and on, and on, and on, with highfalutin buzz on this drug, and yet as we have sat here all day long, what we have seen is a risky venture.

What we have seen is a dearth of information or we have seen lots of sizzle, but not a lot of steak here. So that is what this hearing is all about. How could such a disparity between the promise made to the patients about this drug, and the promise made to the investors, could have existed when in fact just last December this was a fizzling dud?

Ms. KEEGAN. Well, I think there is sometimes a discrepancy between the promise as it may sound to outsiders, and to an oncologist, who would actually find a response rate of 20 percent in patients with no available therapy for colorectal cancer to actually be something of significance clinically and medically.

So if that were in fact the case, I think we would find that probably compelling and that was why we were willing to listen to the company in August 2001 and when we pursued this.

One of the major deficiencies that I see was in the conduct of the clinical trial, and in the oversight of the clinical trial, and in ensuring that the investigators followed the clinical trial, and that the data that the protocol required to be collected, was collected, and that the records were available for review.

I think that was one major deficiency. And as Bristol-Myers Squibb said earlier, that was a basic expectation of Bristol, and that was a basic expectation of the FDA that that would have been done. We did not even discuss that issue. We presumed that it had occurred, and it did not, and I think that is a significant failing that none of us anticipated.

Mr. GREENWOOD. And to what would you attribute that? The thing that is remarkable about this is that if you tell the world that you have in your possession the Holy Grail of cancer treatment, and then when it comes to the conduct of the clinical trials, you have this half-hazard conduct, the two—I can't get these two things to compute. How could that happen? Dr. Pazdur.

Mr. PAZDUR. It is called good drug, bad development plan, and there is nothing that we can do about that at the present time. For example, we may have a meeting with the company, and talk to them about a development plan, and they could walk out of this office and do another development plan if they wish.

I cannot take a gun to somebody's head basically and say you must do what I say here. Nor do I have any recourse to publicly address that issue.

Mr. GREENWOOD. One final question. When the FDA approves of a drug, it is very, very prescriptive in what you may and may not say about the efficacy of that drug, very, very prescriptive. Very complicated labels as to the claims that may be made.

In the period prior to approval of a drug, or prior to the refusal to file a letter of disapproval, it seems that the company can say just about anything. I mean, it seems that the company has this tremendous latitude to say this drug will enable you to fly to the moon and back.

The FDA has some pre-market jurisdiction with regard to such claims, and so could someone help me here with again the discrepancy between—what I am wondering is does the FDA need more power to rein some of these companies in, because a phenomena in which a company pumps up its potentiality to draw investor capital dollars, and to draw in big players in mergers and acquisitions, and so forth, they have tremendous power to do that.

And regardless of whether what they have is really going to do what it says, and very few investors are going to be able to understand the complexities of a cancer treatment. So is there a problem here that the FDA needs to have a little bit more regulatory ability with regard to the claims that companies can make while their product is pending?

Ms. KEEGAN. What I would say is that we actually do have the ability if we believe that somebody is clearly making false and misleading statements. But what we don't have are the resources and the staff to continually monitor for this.

Mr. GREENWOOD. Well, someone said that some of the FDA staff were cringing as they were watching 60 Minutes, and so forth. Were any of you among the cringers watching 60 Minutes?

Ms. KEEGAN. My personal recollection of that 60 Minutes was very much like Dr. Waksal's, which is the focus of that meeting was really on access for patients, and how that was not equitable. I don't recall a lot about things that made me cringe in that.

Mr. GREENWOOD. But what you have said is that if you had more resources and personnel that you could do a better job of perhaps making certain that the claims that are made about pending drugs and other products are reasonably close to accurate?

Ms. KEEGAN. Yes. That is actually done by a different group. I mean, our particular staff are medical officers, and that is not our function. But if there was better resources in order to monitor, I don't think we have a systematic program for doing that. We usually are reactive in that sense if somebody brings a particular claim, or a particular egregious statement to our attention.

Mr. GREENWOOD. Thank you.

Mr. PAZDUR. Here again, most of these are made—most of DDMAC, which handles the advertising, and looks over advertising

of drugs, okay? These claims of pre-approval are usually press releases, et cetera.

And which I am not quite sure how much DDMAC gets into. But we have really no regulatory authority over, I don't believe, of press releases after a meeting with the FDA.

For example, where we could have a very contentious meeting, and this is not uncommon that our medical officers then pull something off Reuters News or something like that, that says that the meeting with the FDA was a very fruitful and productive meeting, which is exactly the opposite of what it was. And we have no way to basically counteract that in essence.

Mr. GREENWOOD. The Chair recognizes the gentleman from Michigan, Mr. Stupak.

Mr. STUPAK. Thank you, Mr. Chairman. But doesn't the FDA get concerned when as in Business Week, the first question I asked today, that this drug was the furthest along of a handful of new cancer treatments that precisely home in on a growth signal found in up to 50 percent of all cancer types? Isn't that an over-hype of the statement?

Ms. KEEGAN. I am not certain that it is. It is the one for which we have had a pre-BLA meeting the earliest, and it does work against the growth factor receptors. So I am not certain what about that statement that you find particularly disturbing.

Mr. STUPAK. Well, in the cancers that we have heard about thus far today is colorectal, and I think there might have been some renal, and there was some questions about neck cancer. There is more than six times of cancer isn't there?

Ms. KEEGAN. That's correct. The epidural growth factor receptor that Erbitux reacts with, and that other drugs are working on, are found on a variety of solid tumors.

Mr. STUPAK. So 50 percent would be a rather misleading statement would it not?

Ms. KEEGAN. I think that is where that comes from, yes.

Mr. STUPAK. So even though you were in the process of doing an accelerated statement, you didn't think the FDA as a public health agency had a right to comment on this?

Ms. KEEGAN. I am not sure that I am finding it to be as problematic as you are.

Mr. STUPAK. Well, maybe we see it as problematic of all the investors, of all the patients, and all their family members who were basically led down the road on this miracle drug that is going to cure up to 50 percent of the growth in cancer tumors in the United States.

In fact, after the USA Today article ran, they were receiving 400 calls a day. I am sure that the FDA must have received at least one call. I mean, I see that you are laughing, but I don't find that a laughing matter.

We are having a hearing because if we are going to have people out there over-hyping their drugs, and the FDA knows that it is not true, and they don't say anything, how does the American people, the investors, large and small, know what the heck is going on here?

And when it shoots up into the top 100 drugs of NASDAQ, that is a concern here. And we look to the FDA, at least us up here,

and some of us who have been on the committee for a while at O&I, to at least set the record straight when misstatements are being made that not only harm people who have cancer, but also investors, and companies, and individuals who may finally put their faith in there because they are at a very desperate stage in their life, especially those who have cancer.

And so I think there is a responsibility here of the lead public health agency in the United States to at least say something, and not just write it off as, oh, well, it is just another hype story.

Ms. KEEGAN. I'm sorry. I smiled because you said you figured that the FDA got at least one phone call, and I am certain that we got way more than one following the publication of that.

I completely agree that it is extremely unfortunate when this information is provided and when cancer patient's hopes are raised. I would say that particularly for pre-market applications that we don't always have all the information in hand, and we rely on the investigators who are publishing results, and on the company who are providing summary data to provide accurate information.

And we don't always have all the information available to know if every statement being made is true or false, and we certainly don't have the resources to review every statement made about every drug in the pre-market phase and determine its accuracy.

Mr. STUPAK. We are not asking for every statement or every press release to be reviewed. It's just that in your area of expertise of cancer oncology—I mean, you are looking at a drug here which is the second most prevalent—I'm sorry, a cancer that is the second most prevalent, and probably one of the most deadliest.

And I think that there is some responsibility there for the FDA to at least when they see, whether it is 60 Minutes, or USA Today, or Business News, to at least say something to inform the public. After all, it is the public that you are supposed to keep foremost in your mind.

Let me ask you this. Fast track. Is it used only for life-threatening drugs, or is it used for drugs where there is an unmet medical need?

Ms. KEEGAN. It should be used for both those conditions; either life-threatening, or serious disease where there is an unmet medical need.

Mr. STUPAK. And fast track has been around since Congress granted it in 1997. Has any other drugs other than cancer drugs where fast track has been used to get cancer drugs up there?

Ms. KEEGAN. I don't know the history of all the others, but I would guess that there are some other drugs that have been evaluated, and AIDS would certainly fall in that classification.

Mr. STUPAK. So AIDS would be one of them. Dr. Pazdur, are there any others?

Mr. PAZDUR. I was just going to say AIDS is the most common one now.

Mr. STUPAK. And that was the one that really spurred the 1997 amendments to PDUFA?

Mr. PAZDUR. Yes.

Mr. STUPAK. All right. There was a pre-meeting of your August 2000 meeting with ImClone, and in the pre-meeting, the primary

FDA medical review officer indicated her reservations concerning the 9923 study, and that is Dr. Jerian. Is that you?

Ms. JERIAN. Yes, that's me.

Mr. STUPAK. Who is part of this team that met in August of 2000 with ImClone?

Ms. JERIAN. This the IND Review Team, which would typically consist of the clinical reviewer, the oncology reviewer, often including the supervisors of those reviewers, and the regulatory project manager. And at times also including the product reviewer.

Mr. STUPAK. So your recommendation that this not be—or at least your reservations, that was shared with everybody was it?

Mr. JERIAN. I shared my opinion about the request of the sponsor at that meeting.

Mr. STUPAK. At the meeting?

Mr. JERIAN. At the pre-meeting.

Mr. STUPAK. And then you had the meeting of August 11, correct, with ImClone?

Mr. JERIAN. Yes.

Mr. STUPAK. And you were there?

Ms. JERIAN. Yes.

Mr. STUPAK. Okay. What transpired and did you change your mind about those reservations at this meeting?

Ms. JERIAN. I did not change my mind.

Mr. STUPAK. Okay. How then was this allowed to proceed then if you did not change your mind? You are the medical officer, and you are the person who is primarily responsible for overlooking this application, or this request for fast track; is that not correct?

Ms. JERIAN. I am the primary medical officer, and I report to my supervisors, and my supervising medical officer at that time during the meeting felt that a different approach would be appropriate.

Mr. STUPAK. Okay. Just one person thought that, your supervisor, or did everyone thing that? Obviously, you didn't, but I mean, did the rest of the people there think that?

I guess I am trying to figure out how did this come about? I mean, you are at a meeting, and you have this memo or pre-meeting at which yo decide that they have to go a long way to convince us.

And you are in the meeting, and you are the primary medical review officer, and they have not convinced you, but somehow they get this application to go forward.

Ms. JERIAN. If I am in a meeting with a sponsor, and my supervisor has made a decision, that person is my supervisor, and I defer to them.

Mr. STUPAK. Okay. So is the decision made upon review of medical or new medical evidence, or just upon hierarchy?

Ms. JERIAN. I would have to defer to my supervisor to answer that question, because it——

Mr. STUPAK. Well, let me put it like this. Was there new medical evidence submitted on August 11, which would change your opinion?

Ms. JERIAN. In my recollection, there was no new medical evidence based on my review.

Mr. STUPAK. Well, your supervisor was Dr. Keegan then, right?

Ms. JERIAN. That's correct.

Mr. STUPAK. So then, Dr. Keegan, why was the medical review overruled if you will, or the supervisor overruled the decision, or the medical review officer's indications?

Ms. KEEGAN. I would attribute it to a difference of opinion in looking at the information. It was my assessment that a drug that is purported to give an approximately 20 percent response rate in patients with refractory disease was something that should be evaluated further.

And we should provide guidance to the company on the kinds of information, and the way they should go about providing evidence to the FDA so that we could consider that and review the data.

Mr. STUPAK. So before August 11 then, did you review the medical evidence that had been submitted?

Ms. KEEGAN. I did not review the entire file. I reviewed the pre-meeting package, which was provided to us, which was the summary data.

Mr. STUPAK. And in that pre-meeting documentation, it had Dr. Jerian's recommendation that we not move forward with this, correct?

Ms. KEEGAN. Could you repeat that?

Mr. STUPAK. Sure. You said that you reviewed the pre-meeting documentation, and you read some of it, and there was a summary, and I expect that would include Dr. Jerian's recommendation that you not move forward with this?

Ms. KEEGAN. Dr. Jerian's recommendations were really verbal. We had a meeting, a discussion, for which there were no minutes kept, and I think the handwritten notes were really her assessment written down, but there was no formal memo written. I think it was just the discussion of the review team.

Mr. STUPAK. Okay. Well, her memo, and her notes from the meeting, state that ORR, overall response rate, equals 15 percent clinically significant for colorectal track—I'm sorry, for colorectal CPT-11 failure, correct? That is one of her concerns, right?

Ms. KEEGAN. Yes.

Mr. STUPAK. Is that correct?

Ms. JERIAN. May I clarify?

Mr. STUPAK. Sure.

Ms. JERIAN. I believe what you are reading from, although it would help if I could see the document, are the questions that the sponsor was asking of us.

Mr. STUPAK. Okay. And then there is another one that says CP02-9923, and that is the protocol that we are talking about, meet accelerated approval criteria in fast track, and then after that it says no. So that would be from your notes, right?

Ms. JERIAN. Those are from my notes, yes.

Mr. STUPAK. Okay. So was it the 20 percent then, because the medical review officer was saying 15 percent; and is it the 20 percent that was in that you decided that we should shoot for?

Ms. KEEGAN. Well, actually, it was the precedent that has been set by the approval of the irinotecan, which was approved on an overall response rate of 13 percent.

And if 13 percent was sufficient to approve irinotecan, it is hard for me to believe that we should judge a much higher standard for Erbitux.

Mr. STUPAK. Sure. Irinotecan was a single agent?

Ms. KEEGAN. That's correct.

Mr. STUPAK. And also demonstrated life expectancy, correct?

Ms. KEEGAN. Not on the original approval. The original approval was based only on response rate information in patients who had failed the available standard therapy. So the setting was very similar in the question being addressed to us.

Mr. STUPAK. Okay. Well, is it fair to say then that you were mislead on the single agent idea that was put forth?

Ms. KEEGAN. By ImClone?

Mr. STUPAK. Yes.

Ms. KEEGAN. I felt that when they told me, or when they told the group at the meeting, that the information in the application would satisfy us, that we would find that compelling and convincing, I felt mislead personally.

That may be a difference of interpretation. They certainly seemed to very much believe that even after we told them that we didn't concur with that assessment.

Mr. STUPAK. So you told them that you didn't concur with that, but they insisted that they could prove this to you on this single agent? You have to say yes or no.

Ms. KEEGAN. I'm sorry, yes. They felt that they could. They felt very strongly that—and they represented to us, to the point of saying that they felt that it would be unethical to conduct a single agent study, and that is where we felt we could not agree with that statement, and why we told them they should do a study.

Mr. GREENWOOD. The gentleman's time has expired. The Chair recognizes the gentleman from Kentucky, Dr. Fletcher.

Mr. FLETCHER. Thank you, Mr. Chairman, and certainly I thank you all for coming. It has been a long day for you, I'm sure. Let me just ask first, and I guess Dr. Keegan, this would be probably addressed to you.

But was this the first clinical drug trial or request for approval of a particular agent from ImClone to the FDA?

Ms. KEEGAN. They have a number of studies in development programs in other cancers, and we had been talking about other development programs. But this was their first approach with a completed study sent that they felt might be reasonable to consider for accelerated approval.

Mr. FLETCHER. Does the FDA, who works with a lot of companies, many like Bristol-Myers Squibb, who had extensive experience with the FDA, and given that, does the FDA have any protocol for new, relatively small, companies that come out to assist them to make sure that they comply with the protocols that they are adequately informed as we go through this process?

Ms. KEEGAN. No.

Mr. FLETCHER. Do you think that would be helpful?

Ms. KEEGAN. I am sure that it would be helpful to the companies. I am not sure how we would accomplish that given our current resources.

Mr. FLETCHER. Let me go back. I believe you were here and you heard Dr. Waksal talk about—and I guess you reported that the discipline of the clinical trial was poor.

And yet we are dealing with the premier institutions in the United States, and probably the premier in the world, and how does that occur, and have you seen this before?

Ms. KEEGAN. I would say that most protocols have a very low rate of protocol violations, but I have never seen a perfect study. The number of deviations in this protocol was out of the norm in my experience, and it exceeded what we expected certainly.

Mr. FLETCHER. Dr. Pazdur, do you have any comment on that?

Mr. PAZDUR. Yes, I do. I have been an investigator for almost 20 years before I joined the FDA at the Anderson Cancer Center, and I have done work in colorectal cancer.

The issue here is the supervision that a pharmaceutical company has to give the sites, and there has to be a fairly frequent auditing of the data by qualified auditors either from the company, or from a CRO, a contract research organization.

I don't know if this was in place since I was not involved with this study, but it is not just the institutions. There is obviously people that are there and variations in the investigators in any institution.

But the overall supervision of a study is the responsibility of the company, and there has to be some type of careful auditing plan. Usually a periodic audit of the data on a monthly, or bi-monthly, quarterly basis, would have caught some of these errors.

So they would not have been problematic and this data would not have been submitted in such poor quality shape here.

Mr. FLETCHER. My understanding is that clinicians do not deviate from requirements based on their best judgment, and that the patient is eligible for the study. Is that a legal requirement?

Ms. KEEGAN. All the investigators who conduct studies under IND sign a statement, a government form, called a 1572, in which they agree to basically conduct the study according to good clinical practices.

It is not enumerated in that, but it basically is a statement that they will adhere to their obligations as a clinical investigator. In that sense, it is a legal requirement. I am not certain that every physician who signs that form understands that, but it is a legal requirement, and a form that they are to sign.

Mr. FLETCHER. Dr. Pazdur, you obviously participated in this. I have been a participant somewhat as a clinician, and more of referring patients, and kind of following them along and training, but we were pretty strict on that, because it is your reputation at stake. And what happened here?

Mr. PAZDUR. I don't know. I don't know. You are entirely right. When you have a protocol, and it specifies the eligibility criteria, a competent investigator should follow those eligibility criteria. It is not a game of chance here.

If it says that a BUN has to be such and such value, then it has to be that value, or less, or greater than a particular value. It is not left up for the judgment of the investigator.

Mr. FLETCHER. Well, there is one patient here, Patient Number 20635, that received the irinotecan for a certain period of time, and there was no CAT scan to evaluate the response during this period. It indicated that as a matter of fact that the CAT scan report on

one cycle of the drug that we are talking about showed that the patient had no metastatic disease at all.

And the question is was this a miraculous cure, or was there any metastatic disease at the very beginning, and that is just very troubling. There is something called a special protocol assessment, and——

Mr. PAZDUR. But could I just—I think what you are pointing to and getting at is that it is sloppy work.

Mr. FLETCHER. Well, that's it, and I have the utmost respect for our institutions of health care in this country, even though a company has the inexperience, and that's why I wanted to ask you about this special protocol assessments.

Is there a mechanism that when you have a company that may have an excellent product, and some very brilliant minds that have developed something, that as they bring it to the FDA that there is some assurance that there are some special protocol assessments that are done to ensure that they are following this protocol?

Because that is in the interests of the patient, and I realize that there is staffing limitations, et cetera.

Mr. PAZDUR. The special protocol assessment isn't to follow a protocol or to audit it as you are suggesting. What special protocol assessments are, are basically we have a meeting with the company, an end of phase two meeting, where we discuss their pivotal registration trials.

Those trials, the written protocol is then sent to the FDA. That protocol is then reviewed in detail. The statistical plan is looked at, and the eligibility plan is looked at. The treatment plan is looked at. They then get a written letter back from the FDA with what the FDA would like to see in the protocol, and what the company would like to see in the protocol. A meeting of minds is had there, and an agreement on a final protocol is established.

The meaning of a special protocol assessment then is that the FDA cannot deviate from its agreement with the company on that unless there is an overwhelming new medical discovery that comes along, or new medical situation.

So it locks the FDA and the sponsor into an agreement, and that has to be so that the FDA does not have the complaint that we are arbitrary and capricious in our decisions, and in our review, and we said this at one time, and we said something else at another time. It locks us into an agreement.

Mr. FLETCHER. Let me ask a couple of other questions. One is do you think—I mean, these are patients where we have to understand from a clinical standpoint that you are dealing with patients who have no other hope.

So there is a strong desire to give them some hope, and if a clinician sees that this medication—I just came from a patient who had a response to this, and it is promising, certainly there would be a great deal of pressure to make sure that this individual was eligible.

You are dealing with real people, and you are dealing with hope where there is no hope. So do you think that influenced the discipline, or the lack of discipline that we see in this study or not? Including the hype about the effectiveness of this drug.

Mr. PAZDUR. Possibly, but we see that in other areas, and that doesn't account for really sloppiness to be honest, and to really evaluate the situation.

There are other mechanisms to avail the patient to therapies, rather than trying to get them in to the protocol in an artificial fashion, and those include a compassionate use program, expanded access program, et cetera.

Mr. FLETCHER. So that is not an excuse for not complying?

Mr. PAZDUR. It should not be.

Mr. FLETCHER. Because actually in the long run from what I understand, you would discredit the trial, which would hurt patients in the future, which is exactly what happened here. Dr. Keegan, let me ask you something.

We have this disparity, in the sense that as a trial is being done, a company has the ability to issue press releases and with the result in this situation of producing a lot of enthusiasm about a drug that may be overstated and maybe not.

But in this case, you all are setting—and I think the chairman mentioned this, you are there watching this happen, and yet one of the requirements or restrictions on the FDA of speaking up when you see this going on, especially—and, Dr. Jerian, you mentioned that you had some concerns about the clinical trial as it goes on.

I mean, are you all restricted from coming out and saying anything? What kind of restrictions do the regulations have? I know that there is some proprietary information that you have that you can't disclose, but what are the restrictions on you all speaking up as you see this disparity of a lot of hype that went on in the ImClone situation?

And do you have a protocol on that? I mean, how do you all deal with this?

Ms. KEEGAN. I don't know that we have an absolute standing operating procedure that is written. If we were to see something very disturbing in the Center for Biologics, because we have a slightly different administrative structure, we would refer our concerns to the advertising and promotional labeling branch, and say we have some concerns about this.

And to the extent that we have in our hands the facts and can document that the statements are untrue, and the statements are very egregious, it is possible that the advertising and promotional labeling branch could write some sort of letter to the sponsor indicating which statements we object to and which we think are false and misleading.

I think we are often hampered in the pre-marketing setting by, one, not actually having the facts and the raw data, and not being able to tell how far off the mark they are, and the others might be ones of semantics. If someone says interesting, it is hard to say that is a misleading statement.

Mr. FLETCHER. In this situation, and I know that the August meeting of 2000 requested fast track, and you felt like the trial was adequate at that time given the fact of a 23 percent response. You didn't feel like a randomized trial was necessary at that time because you didn't want to deprive patients from the medication, and we can understand all of that.

But as things started to unfold did you all become more skeptical of this, and if you did, how much communication was there where you picked up the phone and said, Sam, I think you all are overselling this thing, and you might want to back off?

Ms. KEEGAN. I would say that I think that a reviewer, or an individual could feel that they could make those statements to a sponsor, but that would not carry the same weight as coming to—as a letter or some other action.

However, I think again that the situation was in somewhat a state of flux at the time, particularly during the review as we were just becoming aware of some of these.

And I think that we have spent our focus on assessing the application and not on monitoring the statements that were being made publicly. At least I would say for myself that I really don't on a regular basis review the press releases and the clippings, because I have other things that occupy my time.

Mr. FLETCHER. Mr. Chairman, I certainly appreciate the opportunity. Thank you very much, and thank you all.

Mr. GREENWOOD. The Chair thanks the gentleman. Dr. Mills, when did you come to the realization that the deficiency in the ImClone application were too great and that a refusal to file letter would be necessary?

Mr. MILLS. At the standpoint that there were a number of points, where we were talking with ImClone and discussing elements that we found in the submission which were defective. By November 30, where we had a telecon with ImClone, and discussing some additional elements on that day.

At that time, the number of defects that I had discovered with Dr. Lee Pai-Scherf, such that we both came to the conclusion in that telecon that we felt we needed to recommend to our group that it was time to consider a refusal to file.

When we had just come out of that telecon, we briefed Dr. Keegan at that time, and we gave her the information. She certainly understood our concerns, and she certainly felt that we needed to provide the documentation to her because we were just coming out of the telecon.

In the course of the following week, it was arrived that we were going to refuse to file, based upon that information that we had discovered in the course of the review, and the filing issues.

Mr. GREENWOOD. Did you have a meeting on December 4 with Lilly Lee?

Mr. MILLS. That is correct.

Mr. GREENWOOD. Okay. Now, you were here for her testimony?

Mr. MILLS. Yes.

Mr. GREENWOOD. Would you characterize that meeting in terms of the likely, or how you presented to her the likelihood of various outcomes, because it seemed to me that she was saying that what she came out of that meeting with was that, well, we could get a green light, or we could get a red light, or we could get a yellow light.

The odds are relatively equal that we could get any of those outcomes. How would you characterize that meeting?

Mr. MILLS. I characterized it with Dr. Lee very carefully, that there were indeed four options that could occur. I wanted to main-

tain a very even balance, while I knew that my recommendation and Dr. Pai-Scherf's recommendation to Dr. Keegan a couple of days before was that we should refuse to file it.

I also knew that we had not arrived at that decision as a group, and so, I presented to her in the discussion as it came up, would there be a potential that there would be a refusal to file? I went over the four potential options.

Mr. GREENWOOD. Did you tell her that you had recommended to Dr. Keegan that there be a refusal to file?

Mr. MILLS. No.

Mr. GREENWOOD. Why not?

Mr. MILLS. From the standpoint that that was an internal communication. I did not feel that it was appropriate. If I told her my recommendation at that time, then that would be disclosing information that was informal at that moment with Dr. Keegan one is the supervisor.

Dr. Keegan's decision is what is going to hold the weight. As any of your staff would make staff recommendations from time to time, but you in your situation have to come to that final conclusion.

So I would not disclose to her my internal recommendation, which was still based upon developing information. When I am still in the midst of doing the filing review, I may find additional information which may sway me back.

At this time, though, I knew that I had that concern, that recommendation, but I wanted to be sure to present to her all of her options, and not to overweigh any of the options because I did not represent the entire organization at that moment.

Mr. GREENWOOD. Did she specifically raise the question or ask the question are we going to get an RTF?

Mr. MILLS. That is my recollection of that conversation. She did ask that question.

Mr. GREENWOOD. But you did not assign any probability to that?

Mr. MILLS. No, I did not. I told her and I explained that I could not. That it was the matter of our internal group discussion, and we do have a BLA review committee that is operational here. We also have our own internal organizational structure, a matrix management, where we discuss this and arrive at that type of decision.

I, again, reviewed the four options that could occur from this point, but I was careful to maintain an even weight to them because we had not yet arrived at a decision.

Mr. GREENWOOD. When the RTF letter came out, it had four concerns I think raised about the—well, four reasons why the RTF letter was given. Were those reasons shared with her? Were those concerns that eventually found their way to the RTF letter?

Mr. MILLS. Often——

Mr. GREENWOOD. Were they shared with Dr. Lilly at that time?

Mr. MILLS. I want to be sure in terms of what we were sharing at that time, because it was an ongoing process. It is December 4, and we are going to go to December 28. So issues are coming in as we go.

There was a stream of communications between Dr. Lee, Dr. Pai-Scherf, and myself over the course leading up to December 4. Most of those issues that I was raising with her related to the review of the CT scans and the independent review.

I had carefully documented those and made sure that ImClone was aware of them, and that they were able to give me full input, and to make sure that I was correct in my assessments that these were defects and that they were going to need repair.

In each one of those cases that I had raised, we had communications back from Dr. Lee in the documents that we presented to the committee that indeed that she had agreed, and that they were going to need to be repaired.

Mr. GREENWOOD. By December 4 was it clear to you and was it conveyed to Dr. Lee that more studies would be necessary?

Mr. MILLS. I don't know whether I could determine that more studies would be necessary. But, indeed, it was quite clear that the independent review committee was going to have to be brought back together, and the CT scans were going to have to be reviewed, and that they were going to have to be reassessed——

Mr. GREENWOOD. I am referring specifically to a single agent study.

Mr. MILLS. The single agent study had come in and I believe that we actually had the result come in, and while I have heard December 4 throughout, I believe I knew about that result on December 3.

But that she was aware of that result, and from the understanding that I had, that that was a remarkable piece of information, inasmuch as it had originally been purported to me that Erbitux alone was not going to show any responses.

Mr. GREENWOOD. And finally in retrospect, and in looking prospectively to future applications, one of the things that is particularly troubling about this matter is that this drug had—that it may still hold great promise; great drug, bad study, as Dr. Pazdur said.

Mr. MILLS. Yes?

Mr. GREENWOOD. It had such a hard landing, and when a drug has a hard landing like this, and the stock goes into a free fall, and investor confidence crumbles, and patient confidence and hope crumbles, and so forth, could that have been avoided, and should that have been avoided by the FDA at a date like December 4, saying, look, you might have had this conversation with Dr. Lilly.

You might had said, look, I am going to tell you something, I have recommended an RTF You may want to—I think that is what is likely to happen. I can't be positive because it is subject to review. But you folks may want to pull back and withdraw your application now, and work on some of these things.

And come back with this when you are ready so that your—because you know when an RTF letter comes out, it is a relatively unusual thing, and you know that the impact that is likely to have on the product with such enormous expectations, and this sudden and hard, and devastating landing for the product.

Would it not have been better had you done what I suggested, and that is offered them the opportunity to withdraw their application, and work on it, and come back later to avoid this relatively public embarrassment?

Mr. MILLS. From the standpoint of the four options that I discussed with her, the fourth option that I was clear to remind her of, that in view of the single agent study, Erbitux alone, the result had just come in, plus the findings to date, which showed a number

of things that were going to need to be repaired, and which she agreed to already, that ImClone always has the option to withdraw, and to be able to come back and represent this data. So there were three options that were available to the FDA, in terms of the review, and the fourth option was there with ImClone.

While I made sure that the balance was there, it was remarkable for me at that moment in time, half-way through the review cycle for filing purposes, to be able to tell a sponsor that that is a consideration, and you should consider it in view of everything that you know to date, and especially when you decided, as she had, to come down independently that day unannounced prior to an e-mail coming from her on the train that she would like to meet with us, and that she had had that much concern.

Mr. GREENWOOD. Well, I might question whether in fact your presentation should have been so balanced, when in fact the likelihood in your own mind was that those were not equally likely outcomes.

Mr. MILLS. Well, from that standpoint here, I fully understand your question. Please bear with me, in terms of understanding that I was only halfway through the filing assessment, and I still had to present all of my data and to get confirmation from my organization.

I don't think you want, necessarily, a medical reviewer independently deciding to tell any sponsor that their drug should be withdrawn halfway through the filing, necessarily, without full coordination with the rest of the agency.

And while I might think that my opinion is the opinion, it is an organization that is a matrix, and there are a number of people who have input.

Mr. GREENWOOD. Well, when the team made the decision the next day to go to the RTF, and then there was nearly 3 weeks, or about 3 weeks went by before they got their letter, you did have the opportunity to assertively contact the company and say I am now not compelled to give you such a balanced review, but to suggest to you strongly that your options have narrowed to two; withdrawal or an RTF.

And I would ask the question, Dr. Pazdur, how would your side of the shop have handled it?

Mr. PAZDUR. I think that you really hit upon a very important point here, and that is that there is a high degree of inconsistency on how the agency communicates with sponsors.

And I think that maybe this puts a spotlight on it. And a lot of it has to do with personal preference of the director of the division, for example, and I can't really speak for what goes on in CBER.

For a refuse to file, for example, that we had recently, we took a look at the data, and within 1 week we realized that they forgot to collect an important element, the duration of responses.

So I called up the sponsor and said no way this is going to make it. I am not going to waste our resources reviewing a document when you know that you have a fatal flaw here. Why don't you withdraw it, and you are going to need a new study.

We have meetings before an application comes in and frequently if I realize that there is a fatal flaw in the application, why not ad-

dress it up front with a sponsor and say don't even bother submitting this.

I don't want to waste our review time, our resources. It takes one medical officer on a priority review 6 months basically full-time, and if you already know on a priority that there is a fatal flaw here, why bother going through the mechanics of a review.

So I think in essence that there is a high degree of variability from one division to another. For example, even on non-approval letters, with some companies we may call them up once we have reached that decision and say you have the option. Do you want a non-approval letter or do you want to withdraw the application, and here again there is not a consistent approach within the agency dealing with this, and I think it is a very important element that needs to be addressed.

Mr. GREENWOOD. Dr. Keegan, do you want to say something?

Ms. KEEGAN. Yes. I would agree with Dr. Pazdur that if at the time that we met with the company on a particular product that we felt that there was no way that we were going to be able to approve—for example, if we knew that the major end point of the study, that the primary goal of the study had failed, and that they had not shown what they had intended to show, we would tell a company and that we considered this to be a negative study, that they should not file it and they should not even attempt to submit an application. I think the circumstances here are a little bit different, in that some of the flaws only became available to us as we reviewed the application. And there is a difference in approach here.

We have not to my knowledge in the Center for Biologics in our office called up the sponsor and said we are going to refuse to file this application. Do you want to withdraw.

I think we don't do that for several reasons and I can't speak to all of them because we haven't actually gone through a major discussion, but one consideration would be that such a phone call might to some extent be considered coercive; to call up a company and say do this, and if you don't withdraw, we are sending you this letter. It is a consideration that some people might——

Mr. GREENWOOD. I don't know. I think if someone said to me that you can step off the scaffold, or we can pull the trap door, I think I would like to exercise my options. The gentleman from Michigan.

Mr. STUPAK. Well, thank you. Along those lines then, if ImClone had the inclining that they might get an RTF, did they ever call and ask can we withdraw our drug until we submit further documentation?

Ms. KEEGAN. I was never contacted with a request like that.

Mr. STUPAK. Was anyone?

Ms. KEEGAN. And I don't know of anyone who was.

Mr. STUPAK. And like the FDA, and instead of them taking the positive approach, or however you want to look at it, the approach that maybe you should withdraw, the company also could have requested a withdrawal before that December 28 RTF came out, correct?

Mr. MILLS. I had advised them on December 4 that that was their option, and reminded them that is an option that they can ex-

ercise. Let met emphasize that on December 12 that we had a follow-up telecon with Bristol-Myers, also on the line at that time, where we went through each of the issues again that we had focused on all of the telecons up to that date to make sure and reconfirm each time.

At that time, they were quite aware that these were significant issues, and there were numerous issues, and that they were going to require significant amounts of time to repair.

Mr. STUPAK. Now, the design of the 9923 protocol, that was ImClone's stage two study, correct?

Mr. MILLS. Yes.

Mr. STUPAK. And that was later submitted as a study for this fast track approval, correct?

Mr. MILLS. Yes.

Ms. KEEGAN. What was requested was the portion of the study that met the criteria that we discussed in the August 11 meeting, the subset of the patients in that study, but not the protocol itself, but some modification of that.

Mr. STUPAK. Well, the experts, and I think that Dr. Weiss had talked about this, that the protocol for 9923 was really flawed. In fact, they cite another oncologist that stated, and let me quote, that overall this was a protocol that asked the wrong questions, and then is not tightly written and efficient. The protocol generates far more questions than it could ever answer. It is a blue print for the production of vague answers.

So the protocol from the very beginning had fatal flaws in it.

Ms. KEEGAN. I would disagree with that. I think that there were issues with the protocol that were problematic, but presented with the results of the study, we didn't consider it to be a fatal flaw, but a protocol that didn't answer every question necessary to review the drug for approval.

And that reflects the approach that I recommended that we take.

Mr. STUPAK. If the protocol was not a fatal flaw, then did you, Dr. Keegan, tell them what they had to do to correct 9923?

Ms. KEEGAN. They couldn't correct the protocol after the fact. What we could do is arrive on a group of patients on whom we could assess the effectiveness, the activity, of Erbitux, and that is how I viewed the August 11, 2000 meeting; to determine whether or not there was a significant population.

And we were told approximately 120 patients of the 138 in that study in whom we could assess Erbitux, and we discussed the criteria to be applied for that study, and how we would look at that.

Mr. STUPAK. And actually when you applied the criteria the 138 went down to 89, which then made it statistically unacceptable, correct?

Ms. KEEGAN. That was an issue with the conduct of the study. If in the conduct of the study data were not correct, that is different from the design, and I would just like to make that distinction.

Mr. STUPAK. Sure. And on August 11 when you met with ImClone, you not only met with your officials, but you met also with their consultants, right?

Ms. KEEGAN. Yes.

Mr. STUPAK. And were these consultants of reputable stature within——

Ms. KEEGAN. Yes. Dr. Saltz was their consultant for their colorectal application.

Mr. STUPAK. And did that doctor present some of ImClone's positions to you at that time or were they just there?

Ms. KEEGAN. As I recall, he made the presentation of the study results as an investigator on the study 9923. And then other portions of the presentation were made by various additional members. I don't know if Dr. Mills or Dr. Jerian recollect any differently.

Ms. JERIAN. What I recall of what Dr. Saltz discussed was with what Dr. Keegan mentioned, and in addition when we asked about the issue of single agent use of Erbitux, he expressed the opinion that he felt that it would be unethical to study it as a single agent.

Mr. STUPAK. And, Dr. Pazdur, you said it is a good drug, bad development plan. Is it a good drug or a good idea behind a drug, and a bad development plan?

Mr. PAZDUR. Well, you have to understand that when we see activity, tumor shrinkage, in heavily pre-treated patients, that gives us the initial signal that there is something there to further develop.

I think that this drug has shown some activity.

Mr. STUPAK. For shrinkage?

Mr. PAZDUR. Tumor shrinkage, okay. It's life's story is just beginning basically. What needs to be done is obviously to show that this drug works, and as I stated before, I firmly believe that as it is being done now that you needed a randomized study to show this.

Mr. STUPAK. To show that it works in what way?

Mr. PAZDUR. To show that it works with CPT-11. The clue here, or the major crux of the situation is in that original study with CPT-11, plus Erbitux, do you need the CPT-11 or irinotecan. I have no idea.

And what their subsequent study, the single agent study, was that in order for that to work, you had to have a zero percent almost in the single agent Erbitux study. So in essence they were betting against their own drug to get the combination approved, which is a very faulty design.

And that's why I am saying for a similar study or for a similar drug under development in our center, we have demanded that the sponsor do a randomized study, and work with the sponsor to achieve that, and they did for the exact same indication, a 600 patient study, and answered the question.

So can it be done? Yes, it can be done, but you have to make sure basically that the sponsor adheres to the plan, and for the one indication for this drug, we actually had to work with the sponsor very closely in developing the protocol.

But I guess to answer your question, Mr. Stupak, what I am saying here is that its initial activity is seen, and once these drugs get approved in a refractory setting, they are used in less advanced disease studies.

They are eventually sent into patients that are adjuvant therapy, after surgery and very early staged patients that are at a high risk

for a relapse. And that may even save lives of people who are at high risk for having a relapse after surgery.

So it is a glimmer of activity that needs to be further developed.

Mr. GREENWOOD. The gentleman's time has expired. The Chair recognizes the gentleman from Kentucky, Mr. Fletcher, for 5 minutes.

Mr. FLETCHER. Thank you, Mr. Chairman. Let me certainly thank all of you for coming. Dr. Pai-Scherf, you are currently the medical review officer for Erbitux; is that right?

Mr. PAI-SCHERF. That's correct.

Mr. FLETCHER. And when did you take that position?

Mr. PAI-SCHERF. July 15, 2001, the file was transferred to me.

Mr. FLETCHER. Okay. So you have been through this process quite a bit. Now, as a medical review officer, what are your responsibilities on overseeing this study and the approval process?

Mr. PAI-SCHERF. My responsibility is to review the clinical portion of the BLA.

Mr. FLETCHER. Now, do you get ongoing reports back from these studies? In other words, as the data comes through, I guess you don't get all the data at once. Do you begin to get part of it?

Mr. PAI-SCHERF. The first portion of the clinical studies came in early October, and the final piece came on December 3. So I started my review in early October.

Mr. FLETCHER. And when did you really begin to see that, hey, there are some problems here, or did you see that there were problems?

Mr. PAI-SCHERF. In a very early stage of my review, I noticed some problems, and the first one is that we did not have documentation of the CT scan of the patients receiving irinotecan.

Mr. FLETCHER. So you could not document that they were nonresponders?

Mr. PAI-SCHERF. Yes. Yes, and that was the first piece and a very important piece.

Mr. FLETCHER. And at what point—well, who did you communicate that to?

Mr. PAI-SCHERF. With Dr. Lilly Lee.

Mr. FLETCHER. Dr. Lee with ImClone?

Mr. PAI-SCHERF. Yes.

Mr. FLETCHER. And that was reported that, hey, you have got some real documentation. Did they report back to try to get the documentation? Because that certainly looked to have a significant impact on the refusal to file letter.

Mr. PAI-SCHERF. First she reported that there were 11 patients, and she sent me a table stating that there were 11 patients who were ordered to have a CAT scan, or the physician never ordered, and felt that the patient progressed because of clinical judgment.

Mr. FLETCHER. And that is not adequate for your study at all. I mean, just a clinician's feeling from clinical judgment that the tumor has progressed is not an adequate data collection; is that right?

Mr. PAI-SCHERF. Not for a clinical study supporting licensure, no.

Mr. FLETCHER. Okay. Thank you. In your communication were you at a meeting with Dr. Lee on December 4 when she asked whether the FDA was going to send an RTF letter?

Mr. PAI-SCHERF. Dr. Lee was clearly concerned about all the issues that we had raised at that point.

Mr. FLETCHER. Were you at that meeting?

Mr. PAI-SCHERF. Yes.

Mr. FLETCHER. And so you were at that meeting. Okay.

Mr. PAI-SCHERF. And she stated that—she asked us if there would be an RTF.

Mr. FLETCHER. And what did you say?

Mr. PAI-SCHERF. Dr. Mills answered the question, and I agreed with what he said.

Mr. FLETCHER. Well, you had mentioned that earlier, but go ahead.

Mr. MILLS. From the standpoint again that I offered the four options that were available, three of which were FDA, and one of which was that I offered to ImClone that certainly they could withdraw.

Mr. FLETCHER. Let me ask a question, and I guess it is—I guess this probably goes to Dr. Keegan, but if somebody else has a responsibility, don't hesitate to answer it.

We got testimony earlier from Mr. Bryan Markison that on December 25, of all days, Christmas, that he received a call from someone, and I don't know that we got that individual's name. But he received a call on December 25 that you all were likely—well, not only likely, but that it was going to occur, that an RTF letter would be issued.

And the letter that came out, or at least the one that I see, has got stamped on it December 28. Now, what is the protocol here? Who leaked the information, and is that normal to leak the information, or is that okay to leak the information? It had tremendous impact on the executives, and family, friends, and other folks who ended up selling off a whole lot of stock based on that information.

Ms. KEEGAN. Well, as Dr. Pazdur says, we do have the option, and in his center, he will actually inform a sponsor, a commercial firm, that they would refuse to file the application ahead of issuing the letter.

There is no prohibition against telling a company that you will refuse to file their application. We did not choose to tell them that definitely before we sent the letter, but there is no prohibition against it.

Mr. FLETCHER. Given the fact, and I know that your area of expertise is not that of the SEC, or some of the other things, but should there be something? As someone mentioned, there is no standardization of communications to the companies, and Dr. Pazdur, you may have made that statement.

Mr. PAZDUR. Correct.

Mr. FLETCHER. Should we have some standardization given the impact of markets, the venture capital that is required in the development of these, and obviously the number of investors involved that were affected tremendously by this December 28 letter, and some who used inside information to make a bundle?

Ms. KEEGAN. Well, I think how someone chooses to use the information is not part of our procedure, and certainly any communication that we would provide, we would expect that the company would use it responsibly, or the individuals who received that.

What I would say about standards is that I am not certain. I don't know if it is preferable to companies to be told and to have the opportunity to withdraw. It is certainly something that we could consider.

As Dr. Pazdur says, every office within the Center for Drugs, as well as the three review offices within the Center for Biologics, may differ somewhat in terms of how they might approach that, and whether a standardization is preferable or beneficial, I don't know.

Mr. FLETCHER. Well, let me ask one final or just a few questions. Dr. Pazdur, you mentioned that this is probably a—well, is this a promising drug?

A promising drug class probably, but is it a promising drug?

Mr. PAZDUR. I think it is. I think it is, and what we have seen here as I have stated before is a good drug, bad development plan.

Mr. FLETCHER. What is the time line that you think that this randomized study will come out that this may come back and be issued? How soon do you think we can have this drug, if it is good as you feel it is, and obviously Bristol-Myers——

Mr. PAZDUR. I am not saying that it is as good as it is. I am just saying that it has the potential.

Mr. FLETCHER. Well, if it is 13 percent effective, and people have no other hope, and if it is that in some very recalcitrant tumors, think what it is in some less recalcitrant tumors.

Mr. PAZDUR. You've got it.

Mr. FLETCHER. I mean, you are able to affect shrinkage in tumors that have been resistant to everything. So that is a tremendous potential.

Mr. PAZDUR. Yes.

Mr. FLETCHER. So what is the timeframe that you think——

Mr. PAZDUR. I don't know what the current study is. Pat knows as far as the European study.

Ms. KEEGAN. There is a study being conducted by another partner with ImClone, Merck KGA, and they are conducting a registration trial in Europe that is looking at a randomized trial of Erbitux alone, versus Erbitux plus irinotecan.

That study has completed accrual, and I don't believe that the data are mature enough to analyze at this point. And I don't know the specific timeframes, but the study was conducted and has been completed, but is not yet ready for submission.

Mr. FLETCHER. Would that be submitted to the FDA, or would that be approved only in Europe?

Ms. KEEGAN. No, at the time that we met with ImClone after the refusal to file letter in February 2002, we discussed the source of additional data, and they committed to providing the results of the Merck study to the USFDA and Merck committed to do that.

Mr. FLETCHER. Thank you. Mr. Chairman, I would just like to say in closing that there are several things which I think have been brought to our attention. One is the lack of discipline in this study, even by some of the finest experts in the country, and I think that is shocking.

Second, I believe that the lack of standardization in communication is a real problem here, especially given the market impact that it has, and the financial impact that it has on a lot of investors that were caught unaware.

And so I appreciate you holding this. I think it has uncovered some very important issues that need further work. Thank you.

Mr. GREENWOOD. The Chair thanks the gentleman for his comments, and also for his attendance and participation in the hearing. I would add to that list of policy issues for us to address, and that I think we need to address the question of making sure that there is some process by which the claims of companies who have applications pending can be reviewed, and if necessary, curtailed, and reined in if in fact those are raising expectations that are significantly beyond the expectations that ought to be raised.

Let me clear up just one final piece of information with Dr. Pai-Scherf and Dr. Mills. When Dr. Lilly arrived unannounced or had an unscheduled meeting on December 4, I believe it was her testimony earlier today that she did not initiate the question of are we going to get an RTF letter, and that she just wanted to check on things and see what the options were.

I believe that it was both of your testimonies that she did raise that issue. So you are both nodding your heads?

Mr. MILLS. That is correct.

Mr. GREENWOOD. For the record, since we don't record head nods.

Mr. MILLS. That's right. That is correct.

Mr. PAI-SCHERF. That is correct.

Mr. GREENWOOD. Okay. Thank you. Thank you all for your presence and for waiting to testify, and I thank you for the work that you do on behalf of our country. The hearing is adjourned.

[Whereupon, at 5:03 p.m., the subcommittee was adjourned.]

AN INQUIRY INTO THE IMCLONE CANCER-DRUG STORY

THURSDAY, OCTOBER 10, 2002

HOUSE OF REPRESENTATIVES,
COMMITTEE ON ENERGY AND COMMERCE,
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS,
Washington, DC.

The subcommittee met, pursuant to notice, at 10:10 a.m., in room 2123, Rayburn House Office Building, Hon. James C. Greenwood (chairman) presiding.

Members present: Representatives Greenwood, Stearns, Whitfield, Fletcher, Deutsch, Stupak, Strickland, and DeGette.

Staff present: Alan Slobodin, majority counsel; Anthony M. Cooke, majority counsel; Will Carty, legislative clerk; and David Nelson, minority Counsel.

Mr. GREENWOOD. The meeting will come to order.

Today the subcommittee continues its inquiry into the ImClone cancer-drug story. The purpose of this hearing is to help this committee, as well as the public, understand the circumstances surrounding the Food and Drug Administration's refusal to file the application for Erbitux, a highly publicized cancer drug developed by ImClone Systems, and how the cancer-drug approval system can be improved.

Erbitux initially attracted national attention because it offered new hope for seriously ill colon cancer patients; and because of the premarket publicity about the drug, ImClone's record-setting $2 billion alliance with Bristol-Myers Squibb to market Erbitux, the controversy over the accuracy of ImClone's public descriptions of FDA's concerns in a nonpublic letter and multimillion dollar stock trades by ImClone insiders in the weeks before FDA's negative decision.

On June 12, Samuel Waksal, one of the founders of ImClone and its former CEO, was arrested on a Federal criminal complaint for insider tipping, attempted insider trading, and false statements. In its complaint, the Federal Government alleged that members of Samuel Waksal's family had sold about $10 million worth of stock on December 27, 2001, based on tips by Dr. Waksal the day before the FDA's decision. Dr. Samuel Waksal himself allegedly attempted to sell about $5 million worth of ImClone stock by initially gifting the stock to one of his daughters and having her immediately sell it.

At the subcommittee's hearing on June 13, we heard testimony from one of the committee's investigators and the committee-retained oncology consultant who reviewed some of the data and doc-

umentation from the key study on Erbitux. In addition, Dr. Samuel Waksal appeared and exercised his constitutional right not to testify. We heard testimony from witnesses from ImClone Systems, Bristol-Myers Squibb and the FDA.

Some of the key findings from this hearing were that the primary FDA medical reviewer handling the Erbitux matter did not believe that ImClone's key study met the criteria for accelerated approval and fast-track designation. However, at a meeting between FDA and ImClone in August 2000, the senior FDA medical official in effect overruled the primary medical reviewer and said the protocol design was probably acceptable. The senior FDA official testified that she believed she was misled by ImClone about its claim that a human clinical trial showed that Erbitux had no activity when used alone.

FDA granted fast-track designation to ImClone's Erbitux based on the wrong version of the protocol for the key study and was made before the agency had the single-agent data on Erbitux.

ImClone testified that its officials believed that FDA had accepted the protocol design, that FDA had the correct protocol version and that they were not led to believe that any of the documentation problems and flaws in the studies would actually result in FDA refusing to file the Erbitux application.

On December 24, a law firm retained by Bristol-Myers obtained information from an FDA source that confirmed ImClone would receive a refusal-to-file letter. This information in turn was passed to Harlan Waksal, the then chief operating officer at ImClone, on December 25.

On December 28, 2001, FDA sent ImClone the refusal-to-file letter on the Erbitux application. In subsequent days, Samuel and Harlan Waksal portrayed the reasons for FDA's refusal-to-file letter as based on a lack of proper documentation. However, excerpts of the refusal-to-file letter appeared in a trade publication that showed that FDA's concerns were more serious than just missing documentation and, in fact, raised serious questions about whether ImClone would have to obtain additional data from other preexisting studies or conduct new studies in order to get approval.

The committee's oncology consultant testified that there were serious problems in the key study including high rates of patient ineligibility and waivers. In addition, Bristol-Myers' independent radiology review showed that strict scrutiny of the study data yielded only a response rate of 12.5 percent, less than ImClone's 15 percent goal and much less than the 22.5 percent response rate presented to the public.

Testimony from the FDA officials showed inconsistent approaches on drug product applications and interactions with companies between FDA's Center for Biologics and FDA's Center for Drugs.

Since the June 13 hearing, there have been a number of major developments reported. On June 19, ImClone Systems received a Wells Notice from the Securities and Exchange Commission that appears to indicate that the SEC staff is considering recommending the Commission bring an action against ImClone relating to the company's disclosure immediately following its receipt of the refusal-to-file letter on December 28.

Besides Samuel Waksal and members of his immediate family, other individuals, notably Martha Stewart, have emerged as subjects of investigation for conduct related to trading ImClone stock immediately before the FDA letter was issued. With respect to Ms. Stewart, the committee on September 10 sent a bipartisan letter to the Attorney General requesting his consideration of concerns and information related to statements that Ms. Stewart caused to be made to the committee concerning her trade of ImClone stock.

In August, a Federal grand jury in New York indicted Samuel Waksal on 13 felony counts, including obstruction of justice and bank fraud. Dr. Waksal has pleaded not guilty to these charges.

A few days later, ImClone Systems sued Samuel Waksal for breach of contract and for breach of fiduciary duty based on the company's belief that Dr. Waksal falsely affirmed that he was cooperating with the Federal investigations. FDA granted accelerated approval to a colon cancer drug called Eloxatin. The approval was noteworthy for two reasons. The drug was finally available in the U.S. after being on the market for years in over 50 countries, and the company gained approval by conducting a three-arm randomized trial in less than 2 years with FDA approving the application in 46 days.

An FDA advisory committee recommended approvability for Astra-Zeneca's Iressa based on a 10 percent response rate where the drug was used alone in seriously ill cancer patients who had few, if any, alternatives.

These new developments and additional information obtained by the committee provide the subcommittee with reasons to continue this inquiry and discussion with today's witnesses. For example, the committee has learned that ImClone insiders sold $244 million of ImClone stock in the 2 months before the FDA rejection, and the volume of options trading of ImClone on December 27 and December 28 was unusually high.

This subcommittee is encouraged by FDA's reorganization, but still has questions about how the FDA envisions improving the approval process for cancer drugs. We will also want to hear the FDA's views on the adequacy of its law and procedures on dealing with misleading premarket statements by industry officials to patients and the investing public about data or events contained in confidential FDA meetings and documents.

The subcommittee remains interested in discussing drug approval issues with ImClone, but in addition, this subcommittee will also want to discuss issues bearing on corporate governance. For example, ImClone's legal department told the committee staff that it discovered that Samuel Waksal had forged the signature of ImClone's general counsel in a document certifying Samuel Waksal owned stock warrants that he no longer had. We have also learned that Samuel and Harlan Waksal purchased shredders in January shortly after Sam received a phone call from an SEC investigator.

Many aspects of Samuel Waksal's financial problems and past professional record have come to light. We will want to learn what ImClone's board and management knew about these issues, and when and how these decisionmakers responded.

As the committee continues its inquiry, the picture comes into sharper focus. The ImClone-Erbitux story is truly a tragedy, par-

ticularly for cancer patients and especially those making 400 telephone calls to ImClone daily for compassionate-use access. The evidence shows, in the months leading to the December 2001 rejection, ImClone management spent much of its time nailing down its billion-dollar tender offer with Bristol-Myers, publicizing Erbitux, making millions, but failing to provide the necessary quality control of the clinical package in its application.

At the same time, there appears to have been confusion and miscommunication at FDA. Profits before patients and regulatory incoherence is a betrayal of cancer patients and is at odds with the Federal mission of promoting the public health. Through this accounting of what happened at this hearing, it is my sincere hope that this will enhance the public's confidence in the biotechnology industry and the FDA, and produce a more efficient and effective drug approval process.

I look forward to hearing from the witnesses and working in a bipartisan fashion with my colleagues to produce a better cancer-drug approval system for patients.

The Chair recognizes for purposes of an opening statement the ranking member, the gentleman from Florida, Mr. Deutsch.

[The prepared statement of Hon. James C. Greenwood follows:

PREPARED STATEMENT OF HON. JAMES C. GREENWOOD, CHAIRMAN, SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS

Today the subcommittee continues its inquiry into the ImClone cancer-drug story. The purpose of this hearing is to help this committee as well as the public understand the circumstances surrounding the Food and Drug Administration's (FDA) refusal to file the application for Erbitux, a highly publicized cancer drug developed by ImClone systems, and how the cancer-drug approval system can be improved.

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At the subcommittee's hearing on June 13th, we heard testimony from one of the committee's investigators and a committee-retained oncology consultant who reviewed some of the data and documentation from the key study on Erbitux. In addition, Dr. Samuel Waksal appeared and exercised his constitutional right not to testify. We heard testimony from witnesses from ImClone systems, Bristol-Myers Squibb, and the FDA. Some of the key findings from this hearing were:

—The primary FDA medical reviewer handling the Erbitux matter did not believe that ImClone's key study met the criteria for accelerated approval and fast-track designation. However, at a meeting between FDA and ImClone in August 2000, the senior FDA medical official in effect overruled the primary medical reviewer and said the protocol design was probably acceptable.

—The senior FDA official testified that she believed she was misled by ImClone about its claim that a human clinical trial showed that Erbitux had no activity when used alone.

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believe that any of the documentation problems and flaws in the studies would actually result in FDA refusing to file the Erbitux application.

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—In subsequent days, Samuel and Harlan Waksal portrayed the reasons for FDA's refusal-to-file letter as based on lack of proper documentation. However, excerpts of the refusal-to-file letter appeared in a trade publication that showed that FDA's concerns were more serious than just missing documentation and in fact raised serious questions about whether ImClone would have to obtain additional data from other pre-existing studies or conduct new studies in order to get approval.

—The committee's oncology consultant testified that there were serious problems in the key study, including high rates of patient ineligibility and waivers. In addition, Bristol-Myers independent radiology review showed that strict scrutiny of the study data yielded only a response rate of 12.5%, less than ImClone's 15% goal and much less than the 22.5% response rate presented to the public.

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—On June 19th, ImClone systems received a wells notice from the Securities and Exchange Commission (SEC) that appears to indicate that the SEC staff is considering recommending the commission bring an action against ImClone relating to the company's disclosure immediately following its receipt of the refusal-to-file letter on December 28th.

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Harlan Waksal purchased shredders in January shortly after Sam received a phone call from an SEC investigator. Many aspects of Samuel Waksal's financial problems and past professional record have come to light. We will want to learn what ImClone's board and management knew about these issues, when, and how these decisionmakers responded.

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I look forward to hearing from the witnesses and working in a bipartisan fashion with my colleagues to produce a better cancer-drug approval system for patients.

Mr. DEUTSCH. Thank you, Mr. Chairman. We have two separate panels today, and I think they highlight the two separate trends in our hearings and our investigation.

First, with the head, acting head of the FDA, I think we're here—we will hear an excellent story of really an agency and Congress working very well together, and our staffs, both of our staffs, really doing the work of this subcommittee, really its investigative arm that I think we are so well known and so talented about. And that is—in fact, my understanding is that the FDA has or is in the process of changing its review procedure for human organism drugs to basically—back to the Center for Drug Evaluation from the Center for Biologics. And from all of our understandings, one of the problems of the Erbitux was really a problem—a procedural problem in a sense in terms of the expertise within those two parts of the FDA.

Clearly, there are challenges in that animal studies are different for biologics and chemicals in terms of preclinical trials, but I think our best assessment, as well as the agency's best assessment, is that this review potentially has some very dramatic, positive effects for all Americans and, in fact, all people throughout the world; and so I'm very proud of the work that we've done in a very bipartisan, workmanlike fashion, doing our job.

The second part of the hearing is, I guess, more a step forward in a sense, in our continuing look at some of the corporate disasters that have occurred and looking both at specifics and then systematic issues. I hope that we will focus on systematic issues today, and I think there are some that are clearly there.

In this case, I think the largest focus is really the role of board of directors, in a case where their judgment, in terms of independence, is very much open to question. I specifically—there will be many questions that will come up this morning, but with all that the board knew in terms of Sam Waksal's actions, including—my understanding is the general counsel whose signature was forged will be here—with all of that information available to the board, the fact that the board still did not seek to remove him even at others' suggestion—obviously issues about some of the consulting relationships with the board, really, and the independence.

What I've said previously in other hearings is, even with downturns almost on a daily basis in equity markets, our economy is still by far the strongest economy in the world and the strongest economy in the history of the world, and a lot of that has to do with transparency. And what we've seen, step after step, seem to be problematic issues related to transparency.

To some extent, it is unfortunate that we're doing this in the waning hours of this Congress, because we still have legislation which, hopefully, although it appears more and more unlikely to pass, is trying to protect investors, trying to protect 401(k) owners as well.

Thank you, Mr. Chairman.

Mr. GREENWOOD. The Chair thanks the gentleman.

The gentleman from Kentucky, opening statement.

Mr. FLETCHER. First, Mr. Chairman, I want to thank you for holding this subsequent hearing to the hearing that we had previously. I think as we look—just very briefly, and I'll enter a statement, a little more, later, but it's about patience and investors, public trust.

First, I'm glad to hear some of the changes that the FDA is making in their drug approval process, particularly that some of the problems were uncovered as we looked at the process, the fast-track approval; and also the relationship between the FDA, the SEC, when products are being marketed and statements are being made by companies related to those products that are under review by the FDA.

Second, I think it's very important—and I want to thank the chairman for the second panel as well—corporate responsibility. There are some grave concerns about oversight on the board during all this problem with the approval of Erbitux and ImClone's management. So let me introduce my more lengthy statement, but conclude with that.

And thank you, Mr. Chairman.

Mr. GREENWOOD. The gentleman's statement will be made part of the record, as will any other opening statements that members wish to include in the record.

[The prepared statement of Hon. Ernie Fletcher follows:]

PREPARED STATEMENT OF HON. ERNIE FLETCHER, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF OKLAHOMA

Chairman Greenwood; thank you for having this hearing today.

We have all seen the devastation that Cancer can cause. We know the emotion and physical destruction that this disease brings to patients and their families.

In the US where we have one of the best healthcare systems in the world, there will be more than 1.2 million new cancer cases diagnosed this year alone. This year about 555,500 people will die from cancer.

It is no surprise that patients and physicians are excited when a promising new drug or therapy becomes available. The Energy and Commerce Committee has worked hard to see that groundbreaking research can provide physicians with the tools to provide treatment for cancer.

While new drugs, Like Erbitux show great promise, we must also balance their development with the public's interest—including patients, their families, and investors. They must be proved safe and effective before they are available for general use.

I have deep concerns that ImClone ignored important advice from Dr. Frederick Sparling that the scientific advisory board (SAB) could help the company's situation regarding clinical trials if they would just bring them together to ensure the company could recognize what sound science should look like. I am concerned that the

decision to not bring the SAB together, was made because some on the Board were too close to the clinical trials and Erbitux itself to make unclouded judgements about what were best practices in order to achieve a study void of design and conduct flaws.

At our last hearing, I wanted to make sure that FDA was doing the best job possible to balance these two issues. I still believe we must continue our conversations with the FDA, but I am pleased to see the FDA making some positive changes that will help balance safety and effectiveness. I hope that we can continue to work with FDA to develop policy that allows these new technologies to be available to patients as quickly and safely as possible.

Equally as important, we must look at corporate governance issues such as CEO misconduct, the ImClone insider trading policy, conflicts of interest within the Board and management, and changes in corporate policies made in 2002 in response to this Committee's inquiries, the media attention, and enactment of the Oxley-Sarbanes Act.

It is my hope that many new cancer treatments, including Erbitux can be approved for marketing as quickly and safely as possible. It is FDAs responsibility to maintain the Gold Standard of safety. ImClone needs to recognize that they must not only work to ensure that Erbitux is approved, but also that is safe and effective according to the FDAs standards.

Again, I thank the Chairman for holding this hearing today.

Mr. GREENWOOD. The gentlelady from Colorado is recognized for an opening statement.

Ms. DEGETTE. Thank you, Mr. Chairman. Just to say briefly, I'd like to commend you on holding this hearing today.

Like the other members, I've been quite concerned for some time about what the role of corporate boards has been in all of our investigations on corporate responsibility. And what we've seen over the last year during the hearings of this subcommittee, which have been incredibly productive, we've seen throughout the economy, every industry, from energy to telecommunications to pharmaceuticals; corporate officers, corporate employees almost running rampant with the resources of the company, and the boards just standing by and rubber-stamping whatever these employees wanted to do.

I think that our continuing investigation into board activities and board accountability will be greatly helped by our hearing today, and I just want to thank you for really refocusing this committee's efforts with respect to ImClone on the board activities and also the FDA approval process. I think it will yield a lot of evidence as we move forward to decide what, if any, additional legislation Congress needs to examine to improve the system.

And I yield back the balance of my time.

Mr. GREENWOOD. The Chair thanks the gentlelady.

The gentleman from Florida, Mr. Stearns.

Mr. STEARNS. Thank you, Mr. Chairman, and I commend you for this hearing.

I think many of us have either been on television or heard from the news media. They always ask the question: Congress doesn't need to aggressively inquire into these cases of corporate governance; why don't we just turn these over to the Department of Justice? Why don't we turn them over to the Federal Trade Commission? And my response is that we do have a responsibility here in Congress. We make the laws, both on drug approval and securities trading, and therefore we need to be informed of examples where events do not proceed as the law intended, because we are making the laws here.

One of my concerns was how ImClone was hyping Erbitux on 60 Minutes and the cover of Business Week. Meanwhile, the FDA's hands were tied in not correcting any exaggerated claims made by this company. So, rightly so, we have to explore these, and I think this hearing is important to do that. We'll hear today from the FDA on Federal trade secrecy laws and how they might be permitted to communicate with the subcommittee in such cases where the stock prices have these exaggerated claims.

Furthermore, I'm glad that this committee will again examine these corporate governance issues, because the oversight committee on commerce has the responsibility—and that is what we're elected to do—how directors of companies abuse their positions, get interest-free loans, the CEOs and the like. For this whole system of capitalism to work and the general public to have transparency, we need to have a better understanding of how companies in the biotech industry, like ImClone, work and how we as legislators can make it so it is more transparent to the investors.

Integrity is the elixir that will attract capital and lead to this life-saving innovation which ImClone is trying to do. And to see this poison that is eroding investors' confidence today—so I think this hearing is timely and important, and I commend you, Mr. Chairman.

[The prepared statement of Hon. Cliff Stearns follows:]

PREPARED STATEMENT OF HON. CLIFF STEARNS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF FLORIDA

Mr. Chairman, thank you for holding this follow-up hearing today. On August 25, I was interviewed on MSNBC News, and the reporter asked me didn't I feel that Congress doesn't need to aggressively inquire into cases of corporate governance, that we should just turn these over to the DOJ's antitrust lawyers and the FTC. My response was, and is, that we in Congress make the laws on both drug approval and securities trading, and therefore we need to be informed of examples where events do not proceed as the law intended. And so here we are again.

One of my grievances at the last hearing was how while ImClone was hyping Erbitux on "60 Minutes," and the cover of Business Week, the FDA's hands were tied in not correcting any exaggerated claims made in these features. And rightly so: their role is not as watchdog of the media. I am especially pleased, therefore, that today we will hear from the FDA on Federal Trade Secrecy laws, and how they might be permitted to communicate with the SEC in such cases where stock price may be affected.

Further, I am glad this Committee will again examine corporate governance issues: how directors of companies abuse company debt, get interest-free loans, and the like. For the system of capitalism to work, where the general public invests in private ventures for the betterment of themselves, of the economy, and in the case of a biotech company, the betterment of patients, there needs to exist complete transparency and integrity in a company's operations. Shady executive practices lead to damaging effects rippling through the economy: Integrity is the elixir that will attract capital and lead to lifesaving innovation, while deceit is the poison that is eroding investor confidence. Thank you.

Mr. GREENWOOD. The Chair thanks the gentleman.

The gentleman from Ohio, Mr. Strickland, for an opening statement.

Mr. STRICKLAND. Mr. Chairman, I would like to enter my statement into the record, and I would like to yield my time to Mr. Stupak who has an opening statement.

Mr. GREENWOOD. The gentleman from Michigan is recognized to make an opening statement.

Mr. STUPAK. Thanks, Mr. Chairman. We just called a vote. We're less than 10 minutes, so I won't give my full statement.

First of all, we talked about another hearing. I'm pleased to see that we're having one on Erbitux and ImClone, and the two aspects are how the FDA approves their drugs in the biologics approval and also how ImClone, as a company, failed its investor.

You know, Mr. Stearns brought up the exaggerated claims we heard at the last hearing. Dr. Frank Papineau, who said that—well, the claims may have been exaggerated, and the officials were aware, FDA officials were aware they could do nothing about it because of the secrecy, the trade secrets and stuff of drug applications, he said. I find that sort of just plain wrong. I fail to see how trade secrets are exposed by a simple rebuttal of claims; or at the very least, a statement of caution to the public by the FDA should have been taken. It should have been put out.

After all, the FDA's responsibility here is to protect the health, safety and welfare of the American people. And when exaggerated claims are being made on so-called "miracle drugs," as this was, there should be something there to be able to rebut it; and I hope that is one of the policy decisions this committee will handle.

I also have great reservations about how the FDA handled drug and biologic approvals, and I'm not sure that just switching over to biologics approval to the Center for Drug Evaluation will work. I'll withhold my judgment on that until we hear more about it.

Finally, we've seen in the long series of cases Oversight and Investigation has done, once again a corporate board has allowed its officers basically to take a publicly owned company and use it as their own privately owned piggy bank; and again, I'd be remiss if I did not once again say, I think all this started back in 1995 when we passed a Private Securities Litigation Reform Act that should be repealed.

The Private Securities Litigation Reform Act of 1995 created a permissible legal environment for the threat of lawsuits that were removed and the loser pay—and that law should just be repealed, and I would once again ask the committee to consider repealing the Private Securities Litigation Reform Act.

With that, I'd yield back and submit my full statement for the record.

[The prepared statement of Hon. Bart Stupak follows:]

PREPARED STATEMENT OF HON. BART STUPAK, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Mr. Chairman, we are here today to continue our investigation of the ImClone/Erbitux disaster.

I am pleased we are taking up two very important aspects of this fiasco: how the FDA conducts its drug and biologic approvals, and how ImClone as a company failed its investors.

On June 13, 2002 we had a hearing on ImClone, and I questioned Dr. Frank Papineau, an investigator for this committee and a witness at the hearing, about how FDA could have let ImClone make such exaggerated claims about its drug, Erbitux.

I asked him how it was that the FDA did *not* take steps to publicly correct these misstatements. He replied that FDA officials were aware of these misstatements but could not do anything because of "the secrecy—the trade secrets and stuff of drug applications."

He went on to say that the FDA officials saw the "60 Minutes" story, the USA Today story, and the *Business Week* cover story, and *still* could not say anything.

When I brought up this point to Pat Keegan, the officer who overruled her own staff and allowed the Erbitux application to go forward, she found it amusing and laughed. I do not think this is any laughing matter.Well, this is just wrong. I fail to see how trade secrets are exposed by a simple rebuttal of claims, or at the very least a statement of caution to the public from the FDA.

I have great reservations about how the FDA handles drug and biologic approvals, and I am not sure that switching over the biologics approval to the Centers for Drug Evaluation will work. I will withhold judgment on that.

Today, we are also looking at how the senior officers and board members of ImClone may have worked the system in their favor at the expense of their shareholders.

It appears we have a classic case of corporate malfeasance, although further investigation is ongoing.

What I—and the shareholders who got the short end of the stick—want to know is, "What happened?"

What we do know at this point is that top officers sold large amounts of stock after privately receiving bad news. Stock prices plunged.

It seems as though certain people may have treated this publicly-owned company as a privately-owned piggybank.

I hope this is not what happened.

Perhaps shareholders would have had more recourse if those in Congress didn't strip away their rights in 1995 as part of the Contract on America.

The Private Securities Litigation Reform Act, or PSLRA, stripped away shareholders rights and virtually eliminated deterrence.

It created a permissive legal environment where the threat of lawsuits were removed and the loser pays.

PSLRA should be repealed, and I request the support of my colleagues for my bill that would do just that, H.R. 3829.

Mr. Chairman, I yield back the balance of my time.

Mr. DEUTSCH. Mr. Chairman, I have a statement from the ranking member of the full committee, Mr. Dingell.

Mr. GREENWOOD. Without objection, Mr. Dingell's statement will be made a part of the record.

[The prepared statement of Hon. John D. Dingell follows:]

PREPARED STATEMENT OF HON. JOHN D. DINGELL, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Mr. Chairman, thank you for holding this hearing. As our first ImClone hearing and reports in the press have revealed, this company belongs in the infamous pantheon of firms whose executives have been allowed to treat publicly traded businesses as their own personal cookie jar. Apparently the ImClone Board of Directors, like many others, has been content to take their fees while at best turning a blind eye to abuses that were occurring under their very noses.

This investigation, however, has also addressed another issue of at least equal importance to corporate misdeeds—the efficiency and fairness in the expedited approval process at the Food and Drug Administration (FDA) for drugs to treat illnesses, often life threatening, for which no alternative treatment regime exists.

Congress enacted a process that expedites new experimental treatments to the market in record time, based on very little evidence of effectiveness. Even under these very lax procedures, ImClone was unable or unwilling to undertake the research necessary to make the necessary showing of possible efficacy.

This hurt colorectal cancer patients for whom this drug was the last hope. No drug currently on the market as a treatment for colorectal cancer is much better from a placebo. Even ImClone only claimed its drug, in combination with a chemotherapy agent, shrunk tumors, not actually extended life but shrunk tumors, in less than a quarter of the 120 patients in the study. Analysis of the data by Bristol Meyers put that number at less than 13 percent. The Waksals raised false hopes, and stole the hope that did exist, from those suffering, or whose loved ones are suffering, from this terrible disease.

It appears that the FDA has taken a positive step in the direction of a more rational, consistent approach to expedite these applications. When the reorganization that transfers all drug reviews to the Center for Drugs is complete, all applicants should realize that if they hope to get small Phase II studies considered for early approval, that the science behind those limited studies will have to exhibit the kind of rigor that Dr. Pazdur advocated at our last ImClone hearing.

While this proposed transfer of authority holds the promise of consistency and good science as the heart of expedited consideration, the devil remains as always in the details. Congress, and particularly this Subcommittee, will need to watch carefully. Will needed expertise be transferred? Will bureaucratic delay and uncertainty cause FDA to lose important scientific expertise? Will employee rights be respected? This transfer must be done right, or FDA may make matters worse.

Mr. GREENWOOD. We have just over 7 minutes left in this vote, so the committee will recess and return immediately after the vote.

[Additional statement submitted for the record follows:]

PREPARED STATEMENT OF HON. W.J. "BILLY" TAUZIN, CHAIRMAN, COMMITTEE ON ENERGY AND COMMERCE

Mr. Chairman, thank you and let me commend you and the staff on both sides of the aisle once again for the path-breaking work in this ImClone investigation. There is so much more to this than people just following the news stories over the summer may realize.

Ultimately, this investigation comes down to doing what's right for cancer patients. By exposing the problems that occurred with ImClone's Erbitux and the FDA, you are helping to point the way for us to improve the drug-approval system—to make it work better for these and other patients desperately hoping for breakthrough treatments.

So with all the attention on insider trading and corporate governance—subjects we will take on today as they relate to the problems here—the public should *not* forget that potential flaws in FDA's drug approval process have been at the center of this investigation all along.

These flaws allowed a study of questionable quality to become the basis for fast-track application. They allowed irresponsible hyping of a promising drug as FDA silently stood by—thus raising and dashing hopes of thousands of cancer patients.

I am encouraged that since the June ImClone hearing, the FDA has reorganized pharmaceutical product reviews to enhance consistency and performance. This is a good first step and we are very interested to learn how FDA envisions this reorganization will improve the drug-approval system, especially for cancer drugs. I welcome Dr. Lester Crawford, FDA's Deputy Commissioner, who can discuss this for us.

There's clearly room for improvement. We know this from FDA's own work. Consider Eloxatin. This colon-cancer drug was approved on an accelerated basis by FDA's Center for Drugs on August 12, 2002, within 46 days of submission—a new FDA record. And it was approved based on an interim analysis of a Phase III randomized trial—a trial that measures actual patient survival—instead of less reliable Phase II study-data on surrogate endpoints, which had been the basis for past accelerated-approvals and were the basis for ImClone's application.

Eloxatin shows a company can get accelerated approval just as fast as ImClone had hoped its drug would be approved, and with better data. Perhaps the Eloxatin case can be a useful model for the future. It clearly suggests that ImClone's experience might have been different, if there had been better communication between FDA and ImClone.

I understand that FDA is working on a communications policy that is aimed at improving interactions between the agency and the companies it regulates. This is encouraging and I am hopeful that FDA is moving in a constructive direction.

I look forward to hearing about FDA's views on pre-market promotion or pre-market statements—a topic that also gets to ImClone's actions and governance. This aspect of the ImClone story is essential to our inquiry.

We now understand that ImClone directors and officers reaped millions from the sale of ImClone stock before FDA's refusal-to-file letter. Cancer patients, of course, got their hopes dashed. And what did many ImClone shareholders get from the rejection of Erbitux? An 88% reduction in share price, delay in the development of Erbitux, a CEO—Sam Waksal—who resigned and then was arrested and indicted.

ImClone Systems has now sued Sam Waksal because it believes he did not cooperate with the federal investigations while he affirmed to the company that he was cooperating.

Yet we have now learned that for years ImClone did not trust Sam Waksal with the company's corporate credit card. It actually installed special procedures to ensure he did not charge the company for his personal expenses.

Why would ImClone management have trusted Dr. Waksal?

The media have already reported his financial problems, and his past firings for allegedly misleading and even falsified scientific work. *Fortune* reports that, over

the past 20 years, dozens of lawsuits and tax liens have been filed against Waksal by the IRS, New York State, American Express, banks and brokers, art galleries, contractors, and individuals.

Are we to believe that ImClone management was totally unaware of these issues? Did the Board and management act properly in light of these red flags? We will be interested to hear from the ImClone witnesses on these questions and others surrounding the rejection of Erbitux.

Mr. Chairman, it is my hope that, from this investigation, we will see an improved drug-approval system—where the public has confidence in the companies, the FDA and the companies are clearly communicating with each other, and drug-studies are conducted properly to provide information that will optimize the chances for approval, so patients can be helped.

Thank you, Mr. Chairman.

[Brief recess.]

Mr. GREENWOOD. The committee will come to order. The Chair apologizes for the delay.

And we welcome Dr. Crawford. Thank you for being with us. And I think you're aware that this committee is holding an investigative hearing, and when we hold investigative hearings, we take testimony under oath.

Do you have any objections to giving your testimony under oath?

Mr. CRAWFORD. None whatsoever.

Mr. GREENWOOD. I also should advise you that pursuant to the rues of this committee and the House, you are entitled to be represented by counsel.

Do you choose to be represented by counsel this morning?

Mr. CRAWFORD. Not at this time.

Mr. GREENWOOD. Okay. If it gets dicey and you need a lawyer, just let us know.

Mr. CRAWFORD. We have some waiting in the wings, Mr. Chairman.

Mr. GREENWOOD. All right. In that case, if you would stand and raise your right hand.

[Witness sworn.]

Mr. GREENWOOD. You are under oath, and recognized to make your statement.

TESTIMONY OF HON. LESTER M. CRAWFORD, DEPUTY COMMISSIONER, FOOD AND DRUG ADMINISTRATION

Mr. CRAWFORD. Mr. Chairman and members of the subcommittee, I am Les Crawford, Deputy Commissioner of the Food and Drug Administration. I appreciate the opportunity to address the committee's questions about the agency's communications policy.

The recent announcement of a plan to transfer responsibility for the premarket review of certain therapeutic biological products from our Center for Biologics Evaluation and Research (CBER) to our Center for Drug Evaluation and Research (CDER) and the agency's authority to police the marketplace for false or misleading statements made by companies about their products that are being reviewed by FDA prior to marketing.

In conjunction with the June 2002 reauthorization of the Prescription Drug User Fee Act of 1992, FDA agreed to meet specific performance goals. Under the PDUFA goals, as they are called, CBER and CDER agreed to draft a joint guidance for the agency and industry on how we define good review management principles

for the first review cycle of a new drug application or a biologics license application, otherwise known as a BLA.

At this committee's hearing in June on the subject of the review of the BLA submitted by ImClone for Erbitux, questions were raised about whether CBER and CDER had consistent policies for communicating with sponsors of premarket approval applications. Thus, the importance of this guidance document was highlighted further. This guidance, when finalized, will be based on the agency's best practices for efficient management of review processes and will emphasize the need for effective communications between the agency and sponsors during premarket review.

We recognize the need for guidelines to ensure the consistency of communications. While our overriding responsibility is to help assure the safety and effectiveness of drugs and medical devices, we're also aware that information concerning the status of premarket review and the likelihood of FDA approval can substantially affect the financial markets for publicly held companies.

We anticipate publishing the draft guidance in the next few months and will welcome comments from the public.

As you may know, in September, I announced a plan to transfer responsibility for premarket review of certain therapeutic biologics from CBER to CDER. As part of continuing efforts to improve agency efficiency and consistency, in the fall of 2001, the Office of the Commissioner hired consultants to evaluate the drug review process to identify best practices and make recommendations for improving those processes. The consultants conducted reviews with CBER and CDER staff and reported their findings to me.

Also, during the renegotiation of PDUFA, industry representatives expressed their views to Secretary Thompson and me about the importance of achieving consistency across all review divisions.

Members of my scientific management team gathered data on specific issues of concern and developed a list of options for improving efficiency and consistency at FDA. After reviewing these options, I concluded that CBER performs a variety of functions, such as vaccine and blood regulation, that are distinguishable from the review of most therapeutic biologic products. Furthermore, I concluded that consolidation of certain review functions within CDER would promote efficiency and consistency within the agency.

To manage the transfer of these functions, we have established a team of staff from both centers. The transfer will be accomplished with the greatest attention given to minimizing disruption to current product reviews.

Last, I would like to address questions that have arisen concerning the extent of FDA's authority to take action with respect to false or misleading statements, made by sponsors to the public, regarding products undergoing FDA review.

FDA's paramount statutory mandate is to help assure that patients have access to safe and effective medical products. That is our focus during the preapproval stage. While FDA has authority to correct false or misleading sponsor statements, in appropriate circumstances, primary responsibility for assuring the truthfulness of company statements aimed at investors resides not with FDA, but with the Securities and Exchange Commission.

The SEC has broad authority under Federal securities laws to take action against any sponsor that makes false or misleading statements in connection with a securities transaction. SEC enforcement action based on false or misleading statements to the markets regarding the progress of FDA premarket review is commonplace. FDA has a very effective relationship with the SEC. To further strengthen interagency ties, FDA has taken a systematic review of our interactions with the talented and dedicated people at SEC, and we intend to systematize our interactions further, based on discussions with those individuals.

Thank you very much for the opportunity to be here. I look forward to the further proceedings of this committee.

[The prepared statement of Lester M. Crawford follows:]

PREPARED STATEMENT OF LESTER M. CRAWFORD, DEPUTY COMMISSIONER, FDA

Under the PDUFA goals, CDER and CBER agreed to create a joint guidance for the Agency and industry on how we define Good Review Management Principles for the first review cycle of a new drug or biologics licensing application. This guidance will be based on the Agency's best practices for efficient management of review processes and will emphasize the need for effective communications during interactions between the Agency and industry.

In September Dr. Crawford announced a plan to transfer review of certain therapeutic biological functions from CBER to CDER. FDA has established a team of staff from CBER and CDER to manage this transition.

FDA's primary responsibility during the preapproval stage is to conduct thorough and prompt premarket review of products under investigation. Primary responsibility for assuring the truthfulness of company statements aimed at investors resides with the SEC. FDA has undertaken a systematic review of its interactions with the SEC, and we intend to systemize our interactions further based on discussions with those officials.

Mr. GREENWOOD. Thank you. The Chair recognizes himself for 10 minutes for questions.

Mr. Crawford, on June 27, 2002—in light of the ImClone hearing, the committee sent you a bipartisan letter—I believe it is being handed to you now—asking the FDA to harmonize best practices for designing clinical trial protocols and communications with companies about drug approval issues.

The question is, what action has the FDA taken to encourage more agreements between companies and the FDA about clinical protocol design?

Mr. CRAWFORD. Well, under the recently negotiated PDUFA goals and standards, we agreed that we would engage in a certain number of increased meetings with the industry, meetings that—for which minutes are kept, in which we review what their intentions are, what their progress is, and also offer the best interpretation that we can along scientific lines and medical lines of what we expect the company to do.

These minutes have been referred to in the open press as "contracts" between FDA and the sponsoring firms. In point of fact, they're not, technically speaking, that, but they are an understanding of what the company has to do and also what we expect they will need to do in order to gain approval.

These will be increased, as I mentioned, as a result of PDUFA; and also we are now going to be publishing, as I mentioned, these good review practices for public comment, and that will be part of a larger document where the intention will be not only to systematize, but to bring some consistency between what the different cen-

ters say to the industries that are sponsoring these products, but also from reviewer to reviewer, what is said. And that is a result of this committee's interest and actions and also this letter.

So that will be proceeding apace, we expect, in a very short time, perhaps by the end of the year, that we will have this package out for comment.

We will give a reasonable amount of time for comment, and it also will be submitted to this committee for any action you would like to take, including further meetings with the subcommittees of FDA personnel, including myself and the new commissioner; and we would like to work with the committee on making sure that we refine these practices.

I think it's worth noting that there have always been commonly understood mechanisms and techniques that FDA will use to communicate with the industry. I think it is axiomatic that we have to communicate throughout the review process, because we have to ask them for more information, and they have to——

Mr. GREENWOOD. Let's get right to the ImClone case here, because a number of lay people have said to me, isn't this awful that the FDA leaked this information out that caused the panic at ImClone and the insider trading and so forth? And my response is actually a little different than they expect, because I've been pushing since the mid-90's for more and more transparency at the FDA.

It seems to me that if I look at this particular case, when Ms. Lee was in the FDA's office in—I think it was December 4—at that time, the FDA reviewers with whom she was meeting knew that they had or were about to make a recommendation to their superiors to issue a refusal-to-file letter, and yet that information was not shared with her. And, in fact, there was a lack of transparency from that point forward, except for the fact that the Bristol-Myers lobbyist was able to worm his way in and get some information.

And so it seems to me that cases like that in FDA would be better off—the patients would be better off, the companies would be better off with maximum transparency, so that if companies—so that conversation might have happened where the FDA said, look, we've got some serious—we have some serious problems with your study here. These are what those problems are, and we're inclined to recommend a refusal to file. You should know this. You may want to withdraw your application and do some more work and come back to us, and that might have prevented this very precipitous issue.

How would you respond to that?

Mr. CRAWFORD. Well, I think a couple things, based on that case.

One is, we believe—and it's memorialized in these draft guidances that we're trying to get together as quickly as possible—that the result of the FDA review should be committed to writing. There should be a letter that can change hands, because there were many different interpretations of what was said and who said what, et cetera, et cetera.

So we are moving toward vesting in the division director the requirement that when the decision has been made, to hand out this written statement and I believe that will make for a lot of progress.

Mr. GREENWOOD. Well, but again, that's when a decision has been made.

What I'm talking about is ongoing dialog; and I understand the need to memorialize that dialog in written form so there isn't confusion or there aren't legal concerns. But it seems to me that companies ought to be able to make written inquiries with regard to the status of their applications and receive written responses along—all along the process.

Mr. CRAWFORD. They can and do do that. And I think "written" is a key thing.

The other thing is that although there are certainly early warning signs all along, the final decision on whether or not we're going to file rests with the division director. So theoretically a division director can overturn the decisions early.

So we have to have a focal point for transmitting the information.

Mr. GREENWOOD. Let me get to the question of preapproval promotion, because it's a big issue here.

Without making any judgments about this particular product and how it was promoted and how that compared with the facts, as the company knew them, when a product is approved, it has a very tightly worded label, and it's quite clear as to what claims cannot be made for the product. Prior to approval, there is very little that goes on in terms of the FDA's regulation of what a company can say.

Now, in your opening statement in your testimony, you talked about the SEC being responsible for this, and the status of communications between the SEC and the FDA. Clearly, the SEC is unlikely to have reason to second-guess a company's claims, unless they get some information from the FDA first. SEC has a lot to do and certainly has limited personnel and isn't going to be able to monitor every press release, every printed statement about a potential product.

And there is a lot of opportunity there, putting Erbitux aside for a moment, there's a lot of opportunity to exaggerate claims in order to attract investment.

Do you think that there should be consideration by the Congress of having some review process at the FDA or disclosure process so either the company says, we'd like to make this claim or we'd like you to review it, or we've made this claim and you should see it, so the FDA can monitor and, if need be, refer a case to the SEC?

Mr. CRAWFORD. We'd like to work with the committee on that.

Two quick points: One is that we are—I have asked our office chief counsel the volume of interchange between FDA and SEC, and I'm assured that it is on a daily basis going both ways. So I think this is a case where two executive branch agencies do communicate well.

The second thing is that in the preapproval process, if a company makes some egregious claims that have come to our attention, there are some things that we can do now under the statutory authority that we have. One is that we can send letters, which are commonly called "untitled letters," to the company asking them, in effect, to cease and desist.

If that doesn't work, we can—what we would do historically is send a second untitled letter, and then finally a warning letter.

And it is possible for us legally, if the egregious claims continue, to actually suspend review of the drug.

So we do have that authority.

Mr. GREENWOOD. Let me squeeze one more question in before my time runs out.

What can you tell us about the current status of Erbitux and its review by the FDA, and who is doing—which center is doing the reviewing?

Mr. CRAWFORD. That reviewing is taking place in the Office of Oncology, where it was before. And the second thing is that there are some clinical trials that have begun. And there's one fairly large clinical trial, involving about 300 patients, that is presently under way; and there are a couple more of about 1,000 patients that are being contemplated. And the firm is interacting with FDA in order to be sure that these set up correctly.

Mr. GREENWOOD. Any sense as to when you think the FDA will be—these trials will be completed and the FDA will be in a position to approve or disapprove this drug?

Mr. CRAWFORD. You know, I can't predict. I just can't. Every time I do, I——

Mr. GREENWOOD. Months away or years away?

Mr. CRAWFORD. Let me confer just 1 second.

Yeah. The first review, the first trial, the data should be in by the end of the year. Typically we take about 6 months to review, and we don't know whether the—at the completion of the review, you know, we'll file, it will be approvable, but that would be sort of the earliest, like midyear next year.

Mr. GREENWOOD. Very well. My time has expired.

The gentleman from Florida for 10 minutes.

Mr. DEUTSCH. Thank you, Mr. Chairman.

Dr. Crawford, it's widely alleged that the decision to transfer the review of most biological drugs from the Center for Biologics to the Center for Drugs was not originated from either center, but rather was imposed by the department at the behest of the biotech drug industry.

Without judging that decision, because it's not yet been implemented, I would like to explore how it came about and what preliminary steps your office is taking to see that no requisite expertise is lost from the agency.

First, when and from whom did you first hear this proposal expressed within the government?

Mr. CRAWFORD. When I joined FDA—or rejoined FDA on February 25 of this year, very shortly after that—I believe it was probably in early March—I was briefed about a review of CBER, or a review of their therapeutic biologics, that was going on and that the group that was reviewing it was shortly coming to some conclusions and we might be putting in place a system to develop recommendations based out of that.

There was an internal review committee and also outside consultants that were doing that, and so the—that's the first I would have heard of it.

Mr. DEUTSCH. Excuse me for a second. Who briefed you? Do you recall?

Mr. CRAWFORD. Yes. It was a woman who was in a—a senior associate commissioner named Linda Suydam.

Mr. DEUTSCH. And the outside consultants?

Mr. CRAWFORD. The names of them?

Mr. DEUTSCH. Correct.

Mr. CRAWFORD. I'll have to get that for you. I can submit that for the record.

[The following was received for the record:]

The team included: Dr. Linda Suydam, Mr. William Hubbard; Dr. Theresa Mullin; Mr. Jeff Weber; Mr. Daniel Troy; and Dr. Murray Lumpkin. The outside consultants were Mr. Paul Coppinger and Dr. Elizabeth Jacobsen, who were hired for this task by Dr. Suydam.

Mr. DEUTSCH. Okay.

When did Dr. Woodcock and Dr. Zoon first propose or were informed that they would have to accept this idea?

Mr. CRAWFORD. Dr. Zoon was told that we were considering this around August 1, and she asked for the privilege of responding in writing to the proposal and the idea, which she did.

Dr. Woodcock would not have been informed until after that was done. So it would have been, like, the first of September, somewhere around in there.

Mr. DEUTSCH. And who in FDA and HHS were asked to basically offer opinions on the impact of this prior to the announcement of the shift? Who else did you seek counsel?

Mr. CRAWFORD. Well, the—there is a—I put together a review committee to make recommendations. They were in the Associate Commissioner for Policies' office and also the Acting Deputy Commissioner's office. And the Office of Budget of FDA. There were about 10 or 11. I can provide those names for you if you like.

Mr. DEUTSCH. I appreciate that. What outside groups have been consulted or were consulted?

Mr. CRAWFORD. Groups outside the FDA?

Mr. DEUTSCH. And HHS, outside the government.

Mr. CRAWFORD. When the decision was being made?

Mr. DEUTSCH. Prior to that decision being made, that's correct.

Mr. CRAWFORD. None. At HHS, I conferred with the secretary about what was contemplated.

Mr. DEUTSCH. Okay. So your testimony is that you did not get any outside—I mean, the outside consultants who you used and you would not consider them outside or other——

Mr. CRAWFORD. Well, they were not, no longer employed by the FDA. Both of them had been previously employed.

Mr. DEUTSCH. So we're talking about really two people, two individuals.

Mr. CRAWFORD. Two people and then there was a—the team that was developing recommendations when I got there had conferred with some outside organizations prior to my getting there. And we can get you a list of those if you like.

Mr. DEUTSCH. Okay. But from the time you arrived you didn't interact with anyone.

Mr. CRAWFORD. I did not personally interact with anyone on the outside no.

Mr. DEUTSCH. And just these two consultants.

Mr. CRAWFORD. I did meet with the two consultants once within a few days of my arrival.

Mr. DEUTSCH. And again, you don't recall their names.

Mr. CRAWFORD. I can get those for you.

Mr. DEUTSCH. All right. That's fine. Okay. Throughout the PDUFA reorganization process, FDA repeatedly reminded the Congress that the failure to act well in advance of the September 30 sunset would result in FDA losing a very large investment in human capital as reviewers with expertise leave in the face of uncertainty. What steps has the agency taken to assure that the reviewers will have continuing employment under comparable conditions after this reorganization?

Mr. CRAWFORD. Well, actually, several things both—some before and some after the decision. One is that PDUFA itself in the early passage gave assurance to people who would be involved in this review process that there would be funds enough to keep them on board. As you may recall from the PDUFA hearing, we were concerned that we would have to begin laying off people if we couldn't get the decision before August, or that is late in this legislative year. Since that time we have identified key personnel that may be leaving, and we have the authority now to offer them incentives to stay, that is monetary incentives to adjust their salaries, and then I get a weekly report on movement of personnel and I attempt to be very careful about unusual changes.

So far we have not—once PDUFA was signed and presented, we have had very few losses.

Mr. DEUTSCH. Okay. I understand what you just said. I am told that Dr. Zoon has said that she is already losing top people. Would you say that is not accurate, inaccurate or maybe not to your knowledge at this point?

Mr. CRAWFORD. There haven't been any unusual losses. FDA has an annual turnover rate of about 8 percent, and the record shows that's continuing.

Mr. DEUTSCH. Okay. Thank you. Thank you, Mr. Chairman.

Mr. GREENWOOD. The gentleman from Florida is recognized for 10 minutes.

Mr. STEARNS. I thank the chairman.

Dr. Crawford, when ImClone was hyping their—the drug Erbitux, Erbitux, were you familiar with their hyping? Did you know of their hyping?

Mr. CRAWFORD. Unfortunately, Mr. Stearns, I was not there at the time.

Mr. STEARNS. Okay. Did your predecessor know of it? Did he ever say to you boy, these folks are really hyping this drug.

Mr. CRAWFORD. I didn't come until late February, so I would not have had any interaction. I did talk to my predecessor about the major items that were developing and had developed during the year that he had been acting commissioner and that subject did not come out.

Mr. STEARNS. So nobody in the FDA ever talked about ImClone hyping the drug Erbitux?

Mr. CRAWFORD. They did not talk to me about it no.

Mr. STEARNS. They did not talk to you. And you had no—to your knowledge, you had no awareness that there was hyping going on at ImClone?

Mr. CRAWFORD. Well, had I been there, I may have known about it. But I wasn't there.

Mr. STEARNS. No, I mean after you were appointed and once you were there, no one ever talked to you about it? It was never a subject and no one said, you know, as a result of this, we should do some new procedures.

Mr. CRAWFORD. Actually, I believe that the procedures that I discussed earlier may have emanated from that, and I have reason to believe that they did. I'm just—you know, there was no specific conversation where someone said to me, because of that incident we need to push these forward. However, I do believe that the procedures that are now in draft form will help and I think they are part of that. I don't dispute that at all.

Mr. STEARNS. Yeah. What I'm trying to establish with this line of questioning is that the new procedure established because of ImClone's hyping the drug, one of the reasons these procedures have been established. Do you think that's fair to say?

Mr. CRAWFORD. It would be surprising to me if that was not the case, yes.

Mr. STEARNS. Okay. Once the FDA is doing their pre-new drug application, they meet with a drug company and get an opportunity to sell the agency, you know, the company meets with you folks and has an opportunity to sell you on it in the pre-new drug application. But after the application is submitted, explain to me the opportunities that they have for face-to-face meetings with the company. Okay.

Mr. CRAWFORD. Well, they—we hope they sell through science, I mean it's a form of selling, but we do, from the very beginning, have an understanding with them of what will be expected in order to get the claims that they're seeking. It has to be first a decision about what the drug will be used for and what the claims will be. Their opportunity to meet with FDA is unfettered. Prior to the Prescription Drug User Fee Act, I am told that that was a problem in terms of resources. But the passage of PDUFA and the utilization of some of those funds for this activity has improved that remarkably. So I don't believe anyone is being denied a meeting. There are a great number of meetings, and we can provide that for the record if you like.

Mr. STEARNS. I guess what we're trying to also establish on this committee is sort of the vision for improving the whole approval process for cancer drugs. I mean, ImClone is one example, but we're trying to put in place procedures so that these things are expedited. You know, and lots of us feel that the FDA sometimes moves slowly on this process. Do you think that there's a way to expedite this anyway if we have more face-to-face meetings between the company and the FDA? I mean, all—and a little bit in ImClone's defense, they want to know what's going on. They don't know what's going on. They want to, you know, they're sitting there waiting and waiting and waiting. Obviously, they shouldn't have been hyping it. But on the other hand, at the same time more FDA face-to-face meetings would have been helpful.

Mr. CRAWFORD. They had access to face-to-face meetings and these were regularly held. As I mentioned, under the Prescription Drug User Fee Act, we have resources that are expended for these meetings which are resource-intensive, to be sure. And they take a great deal of preparation and a great deal of follow up. But that is happening. And we are also emphasizing that cancer drugs are important. I believe that they get as good a treatment as any compound can. They also can get special consideration for fast track approval and also for accelerated approval. The company has to ask for that. In terms of fast track, we determine if their request is present, they make the request and if we can find some plausibility of approval and usefulness for an unmet medical need, they get top-of-the-line coverage, and also top-of-the-queue coverage.

Mr. STEARNS. So they simply have to just ask for fast track.

Mr. CRAWFORD. They have to ask and then we have to evaluate whether or not it truly is for an unmet medical need. And if there is plausibility of its usefulness and approval. But if it—and if they don't ask, you know, we sometimes can suggest that they might ask.

Mr. STEARNS. I guess there's a question whether the FDA spelled out the consequences of a single agent study results to ImClone. If the agency asks the company to conduct a study in support of an application, how can the agency communicate clearly to the company what will happen in the event of certain results?

Mr. CRAWFORD. Well, that's the creative tension that we have with the manufacturer. We tell them what they have to do, sometimes they disagree. They can—you know, it's a free country. They can go ahead and do whatever they want to do. And they're not obligated to follow FDA's advice. In most cases, companies do. But there is a give and take. I don't want to, you know, confuse anyone on that notion. We could be wrong. The company could say, well, why don't we do it this way. Why don't we do this trial, why don't we do this study in animals or whatever. And FDA can be convinced that that is the proper way to go.

Mr. STEARNS. Yeah. So in conclusion, you basically agree that the idea that the FDA should have periodic face-to-face meetings with the companies during the review process.

Mr. CRAWFORD. I do.

Mr. STEARNS. And do you think they should be spelled out in a little bit more detail. Or do you think——

Mr. CRAWFORD. This new package that we're putting together called good review practices——

Mr. STEARNS. Because every reviewer is different, you know. This reviewer could have this idea, this reviewer could have this idea and so I mean, do we need a consistent policy where we say this is what should be done so that the companies know.

Mr. CRAWFORD. We do and we're doing that. We're going to put it out for public comment by the end of this year. Consistency among reviews, as you have pointed out, is one of the great management challenges at FDA.

Mr. STEARNS. Okay. I thank the chairman.

Mr. GREENWOOD. The Chair thanks the gentleman from Florida. The gentlelady from Colorado is recognized for 10 minutes.

Ms. DEGETTE. Thank you, Mr. Chairman. Dr. Crawford, in our last hearing on this whole issue, we talked a lot about the fast track drug approval process that the FDA's been using for certain drugs for a while, and then which Congress codified and expanded on in 1997 and what the standards are for approval of drugs under that process and how it differs from the regular approval process. And I guess I would like for you to talk for a minute about how the FDA is viewing the fast track approval process and how it's working and how—how it's working differently from the regular drug approval process.

Mr. CRAWFORD. The regular drug approval process is best described as a first-come/first-served process. What fast track does is it enables compounds of special promise to get to the top of the queue. And I think everyone would agree that it is a necessary and useful procedure and policy, and the codification of that was welcomed.

Ms. DEGETTE. And in general, we all—and I supported it too. Our thinking was with fast track, is that it would be particularly useful for drugs used for diseases, like in this case, the Erbitux, which was to be used for colorectal cancer, where there are not very many options for the patients who have this type of cancer; is that accurate?

Mr. CRAWFORD. That is accurate, yes.

Ms. DEGETTE. But is it your sense that because it's used for these types of drugs, that the clinical trial standards should be different from those used in the regular FDA approval process?

Mr. CRAWFORD. No.

Ms. DEGETTE. Okay. So your sense is then—and is this a view shared throughout the FDA?

Mr. CRAWFORD. Yes. It's FDA policy.

Ms. DEGETTE. Okay. Because we kind of got the sense in our last hearing that because Erbitux was part of a fast track drug approval process, that the clinical trial standards would be, you know, fudged around the edges a little bit because it was an experimental drug being used for a serious disease that doesn't have very many options.

Mr. CRAWFORD. Well, the time saving is in expeditious review, not in shortening of the studies.

Ms. DEGETTE. Right. I mean, what we learned in our last hearing was that for Erbitux, for example, the FDA approved a clinical trial process that actually had a much smaller sample size than under the normal process. Were you aware of that?

Mr. CRAWFORD. The sample size is, in effect, negotiated. The company proposes what the studies will look like and FDA interacts with them and has—is not directly related to fast track.

Ms. DEGETTE. Were you aware that the clinical trials had already been completed by the time Erbitux was put on the fast track approval process?

Mr. CRAWFORD. I wasn't involved in the review. I can check that out for you. And I wasn't even in the agency.

Ms. DEGETTE. I'm pretty sure, from our last hearing, that that was the case. So what you're saying is at least from your perspective, during this negotiation process between the FDA and the developers of the drugs, they shouldn't be allowing for smaller sample

sizes just because the drug is going to be subject to a fast track process?

Mr. CRAWFORD. Well, the standard is whatever they do has to be statistically significant. In other words, you have to be able to induce from the trial that there is an improvement. And that—that's not necessarily referable to the numbers of patients that are in the trial. It's referable to what the data needs are.

Ms. DEGETTE. I understand what you're saying. But what we heard in the last hearing was when they went back, I mean—and this is sort of what happened in this case. When the FDA reviewers went back and looked at the original studies, they realized not only was the sample size smaller than in a normal study, but also that the individuals involved in those clinical trials a lot of times, didn't fully meet the requirements of the study. Were you aware of that?

Mr. CRAWFORD. I wasn't here then and I was not a reviewer. I can look that up for you.

Ms. DEGETTE. Okay. You have not become aware of that since then?

Mr. CRAWFORD. No.

Ms. DEGETTE. But it would be your testimony that fudging like that, allowing a smaller-than-normal sample size, allowing within that sample size folks who maybe weren't completely qualified to be in the clinical trial, that would not be contemplated by the FDA fast track approval process.

Mr. CRAWFORD. My testimony is that fudging is not allowed.

Ms. DEGETTE. Good. And I think that's really important because one thing we are trying to investigate in this committee is how all of this happened. And one thing that some have said is that part of the problem was communication between both CBER, CDER and who should be responsible for, you know, for undertaking these studies. And so I guess my question would be—I know the FDA announced in early September it would transfer the review of certain therapeutic biologies from CBER to CDER which has more experience. And my question is, how do you think that this will improve the communication process and maybe even the approval process.

Mr. CRAWFORD. Well, we haven't worked out the implementation details of that. These should be ready very soon, however, and I can submit that for the record. The idea is that if you consolidate similar review functions within one unit, then you should get more efficiency. And so it's a move toward efficiency.

Ms. DEGETTE. Would it also improve the scientific accuracy?

Mr. CRAWFORD. Well, the Center for Biologic Evaluation and Research is a highly respected organization, and there is no supposition on my part or anyone else's part that they didn't do a first-rate job. But if you're doing essentially the same thing at two different centers, you ought to be able to get it done more efficiently, not more scientifically but more efficiently if you consolidate it in one other center. To some extent, although the decision to consolidate has been made, exactly what will be consolidated is still being considered.

Ms. DEGETTE. And how long will that take to decide?

Mr. CRAWFORD. It'll be done by the end of this year, and should be done the first—the things we can share with you about our con-

clusions of this implementation group will be within a matter of a very few weeks.

Ms. DEGETTE. Mr. Chairman, I'd ask that we submit—we supplement the record with that answer.

Mr. GREENWOOD. Without objection, we will.

[The following was received for the record:]

The CBER/CDER Product Consolidation Working Group (the Group) discussed Phase 1 of the implementation plan relating to the scope of products to be consolidated. The Group's October 28, 2002, memorandum is set forth in Enclosure A. [Enclosure A appears at the end of the hearing.]

Ms. DEGETTE. Thanks. Okay. I have one last question which I intend to talk to the board about as well. We're concerned on this committee a lot about conflicts of interest in medical research. There are institutional conflicts of interests, principal investigator conflicts, and the question we have is is this affecting the integrity of medical research? And in this instance, it's particularly troubling because Dr. Mendelsohn, who's the inventor of Erbitux, not only also sits on the ImClone boards of directors, but also heads the M.D. Anderson Cancer Center in Houston, which is the same cancer center that serves as a clinical trial site for Erbitux.

And the problem that we have, and that I have, is that M.D. Anderson failed to inform patients that were participating in clinical trials that Dr. Mendelsohn stood to make $6 million from the drugs' success. So my question is, in 2001, the GAO called on HHS, including the FDA, to promulgate new regulations to issue guidance to address institutional conflicts of interest. By the way, this is something I'm working on in general in a clinical trial bill that I'm working on.

What the GAO said was that institutional financial interests may color an institution's review, approval or monitoring of research conducted under its auspices or its allocation of equipment facilities and staff for research. And then just a few weeks ago, the American Association of Medical Colleges issued its report on institutional conflicts of interest and recommended full disclosure in situations like that that faced M.D. Anderson. So my question is, what is HHS, and most specifically, FDA, doing to address institutional conflicts of interest?

Mr. CRAWFORD. The Department of Health and Human Services has, at the departmental level, an organization called the Office of Human Research Protection, and they're dealing with this and some other items. Let me—if I could confer for just a moment.

Ms. DEGETTE. Thank you.

Mr. CRAWFORD. Yeah. They're looking at conflict of interest in a very broad way, and I think—I have met with that group several times since I've been at FDA. And the specific issue that you're mentioning, that is someone being connected either on the board or an officer with a clinical center that's doing the investigation, will be encompassed in what they're considering. But what I need to do is to get the minutes of our meetings and submit that as part of the record.

I also would—with your permission, I also will get a report from that office. They don't report to FDA. They rather—we'd rather report to them. So if that's okay, I'll make sure that their deliberations are made part of the record.

[The following was received for the record:]

The Department has been considering the issue of the effect of financial interests on human subject protection for several years. In August 2000, the Department sponsored a conference on this subject. FDA had an integral role in the planning and conduct of that meeting, which led the Department to issue for public comment a draft interim guidance entitled, "Financial Relationships in Clinical Research: Issues for Institutions, Clinical Investigators, and IRBs to Consider when Dealing with Issues of Financial Interests and Human Subject Protection." This document was available to the public on January 10, 2001. Following the issuance of the draft interim guidance, a number of other public and private organizations began to examine these issues, leading in some cases to the publication of reports or policies. The public bodies that have addressed financial interests in research include the National Bioethics Advisory Commission, the HHS Office of Inspector General, and the General Accounting Office. Private organizations that are examining these issues include the Association of American Universities, the Association of American Medical Colleges; the American Medical Association; and the American Society of Gene Therapy. Also, on September 30, 2002, the National Institutes of Health sponsored a workshop at which issues Related to institutions were discussed. FDA and the Department continue to work together to address conflicts of interest in research and the protection of human subjects.

Ms. DEGETTE. Yeah. Again, what kind of timeframe are they looking at as they look at promulgation of ethical standards?

Mr. CRAWFORD. They—I don't set their timeframes. But my sense is that there's great urgency about it.

Ms. DEGETTE. That would be my sense, too. Are you concerned about this issue?

Mr. CRAWFORD. I am.

Ms. DEGETTE. And can you tell me why you're concerned about it?

Mr. CRAWFORD. Well, I think there are several—there a couple of ways to look at these kind of things. One is actual conflicts of interest and perceived conflicts of interest. And full disclosure is what I've always been in favor of. I was editor of a journal before I took this job. And we required the listing of on every publication and everything of whether or not a person did have conflicts of interest. They could self-declare, and we also could challenge.

And in the center I directed at Georgetown University, we did the same kind of thing. So I am—you know, I'm on record as favoring full disclosure of conflicts of interest and possible conflicts of interest.

And I think there has to be oversight of that. I think you can't depend on the investigator themselves.

Ms. DEGETTE. And that would help the FDA in reviewing applications as well if the clinical trials were being undertaken at some place where there was a board member or someone who had a financial interest?

Mr. CRAWFORD. Absolutely. I fully agree.

Ms. DEGETTE. Thank you, Mr. Chairman. I yield back.

Mr. GREENWOOD. The Chair thanks the gentlelady. Mr. Crawford in your response to a question I asked earlier about Erbitux particularly and its status, I believe you said that it was still at the Center for Biologics which is doing the review; is that correct?

Mr. CRAWFORD. I'll have to check where it is. That is correct, yes.

Mr. GREENWOOD. The question then, is it—is this application going to be transitioned over to the new combined center or to the pharmaceutical center?

Mr. CRAWFORD. My decision on that has not been fully reached. We have—those that are under review at the present time, I would have—I would want to make sure that they did not leave the unit that is being—doing the review. I think it is important to note that the entire unit would transfer under one scenario to the Center for Drug Evaluation and Research, so there'd be no disruption.

Mr. GREENWOOD. Well, who has signatory authority on oncology products at CDER now?

Mr. CRAWFORD. The director of the division of oncology.

Mr. GREENWOOD. Is that Richard Pazdur?

Mr. CRAWFORD. It is.

Mr. GREENWOOD. And who is going to have signatory authority on oncology products after the transfer.

Mr. CRAWFORD. It would be him.

Mr. GREENWOOD. So, what issues does FDA have to resolve first before implementing this reorganization? What do you have to do?

Mr. CRAWFORD. What we did was to put together a task force of personnel from both centers to hear about what categories of compounds should be transferred and what special considerations so that we don't delay the process, would come to the fore. Basically, it's to be sure that we don't lose efficiency by trying to get more efficiency.

Mr. GREENWOOD. So why don't you just briefly outline what you think the advantages will be of this reorganization.

Mr. CRAWFORD. The advantage will be that in the Center for Drug Evaluation and Research, there is expertise and also a unit that reviews drugs that are very similar to these therapeutic biologics. And so since they already have the unit set up and since it's functioning, if you put these in there, you would—you should get more efficiency because you have a critical mass. When you have review units you have to have statisticians. You have to have pathologists, biochemists and so forth. And so what we're trying to do in FDA and have been for some time is not have to recreate this critical mass of expertise in order to get the job of review done. And when that has been done correctly, we have experienced efficiencies.

Mr. GREENWOOD. Back to this question of communication with the sponsors, communications back and forth between FDA and the sponsors, the question I have really is do you think it should be the policy that the sponsor—if the sponsors wants a face-to-face meeting, that that ought to be the sponsors' right? In other words, that it's not simply at the subjective decision of a particular reviewer as to when and how frequently those meetings should occur.

But it seems to me that we still don't have the policy and I haven't heard you describe yet this morning a policy in which that would be the rule.

Mr. CRAWFORD. The policy is being developed and we, as I mentioned, we are going to submit that to the committee as well as ask for public comment. It is my feeling and it is FDA policy that the sponsors do have the right to have these meetings. Of course, they have to be scheduled correctly. You have to make sure that you have the right people at the meeting, both from the company's side. They can't just—there was a time actually when I was first at FDA in the 1970's, when sponsors of the center I directed at that time

could just, as we put it, fall in off the street and come by and see you and those meetings were better described as lobbying meetings than scientific interchange meetings.

So we've come a long way since then. There has to be some order in the process. But meeting with the reviewers is the right that the companies have and should expect to exercise.

Mr. GREENWOOD. Okay. And that sounds like the right policy to me. The Chair recognizes the gentleman from Michigan, Mr. Stupak for 10 minutes. And let me announce so that everyone knows what's going on. I know you have scheduling issues. At the conclusion of Mr. Stupak's time, oh and Mr. Whitfield is here. And if he has questions at the conclusion we will break until at least 1 for lunch and then we'll take panel two.

Mr. Stupak.

Mr. STUPAK. Thank you, Mr. Chairman. I apologize. I missed most of this hearing. I've been over in the Senate and I appreciate the chairman's indulgence, and hopefully none of my questions are redundant.

Dr. Crawford, you said in your statement that it is not the FDA's responsibility to correct false and misleading statements to the public by a drug sponsor. Rather, you state it's the SEC's responsibility to do this. Do you, or have you communicated your concerns with the SEC?

Mr. CRAWFORD. Yes. In preparation for this hearing, I asked of our Office of Chief Counsel to give me an understanding of how frequent and how productive our communication was with the Securities and Exchange Commission and on the productivity scale, it's reported to me that it is very productive, that these are actually two executive branch agencies that interact well with each other. Their frequency of contact is daily on both sides. They initiate contact with FDA on subject matter areas, and we initiate them also. So it's working.

Mr. STUPAK. But what about specifically on false, misleading statements where the SEC should step in? And has those communications been since the last hearing, which was, I believe, in June?

Mr. CRAWFORD. Yes. We've had those kinds of communications with them. I can give you some statement of how many, if you would like for the record.

Mr. STUPAK. Well, at these communications have you come up with any kind of solution on how you're going to resolve this situation?

Mr. CRAWFORD. We have. We have—we're developing a document called the Good Review Practices Document, which does address this issue and we're—we're going to put it out for—we're going to supply it to the committee and also going to put it out for public comment. It's in—fairly far along in development, and we'll have that done by the end of the year. And it will address this so as to routinize these kinds of interchanges. It will also routinize other things, like how reviewers interact with the sponsoring drug and biologics firms likewise.

Mr. STUPAK. Okay. You also stated, I believe, in your statement that the FDA currently does have authority to correct misstatements. What kind of situation would lead to the FDA to step in or take an active role in correcting misstatements? In other

words, what would it take for the FDA to step in? I mean, here we had a drug that was called the miracle drug in Business Week, I believe, 60 Minutes. In fact, I think in the June testimony, some of the FDA people said they were appalled at some of the statements being made, but yet they said and did nothing. So what does it take?

Mr. CRAWFORD. You mean, in the pre-approval timeframe before it's on the market?

Mr. STUPAK. Sure.

Mr. CRAWFORD. What we can do, obviously SEC reference is one thing. But FDA also has authority to do the following things, and we have done these in instances in the past and up to the present. And that is, we are—we send to a company that's making egregious claims in the pre-approval era period what's called an untitled letter. And in those letters, we indicate what we find unacceptable about the issuances that they're putting out, and we also call upon them to cease and desist doing that. If the untitled letter does not bring relief, then we go, at some stage, to what's called a warning letter. And the warning letter informs them that their behavior is unacceptable and could result in the suspension of the review process for the product that's under consideration.

Mr. STUPAK. In the matter before us, Erbitux, did anyone send an untitled letter?

Mr. CRAWFORD. I was not at the agency at that time. But let me check. I'm—we're not aware of one.

Mr. STUPAK. So in this case, basically, despite the claims and people were appalled from the FDA, nothing was really done on this one then, right?

Mr. CRAWFORD. We're not aware of that being done, no.

Mr. STUPAK. Okay. When you do these untitled letters, with a cease and desist order or statement, whatever you want to call it in the untitled letter, do you inform the public of it?

Mr. CRAWFORD. Those are available under the Freedom of Information Act. We don't normally do that.

Mr. STUPAK. But the people would have no way of knowing.

Mr. CRAWFORD. We do not suppress that information.

Mr. STUPAK. Sure, if someone asked for it.

Mr. CRAWFORD. Asked for it.

Mr. STUPAK. But the public probably didn't know to ask for it until today.

Mr. CRAWFORD. I'm informed that our new policy that has been developed is that we post them on the Web site. Now, we don't tell people though that they're on the Web site. You have to look on the Web site.

Mr. STUPAK. So when you post it on the Web site, you don't put out a press release or anything like that?

Mr. CRAWFORD. No.

Mr. STUPAK. Okay. And again, posting on the Web site is that post June 2002, after our last hearing?

Mr. CRAWFORD. Actually, we're trying to go electronic and I think that—that's been done since about 1996.

Mr. STUPAK. Okay. You indicate that after the untitled letter, and it wasn't done in this case, but in other cases that's been done,

and then there's a warning letter. And then if necessary, you can spend time to review the application; is that correct?

Mr. CRAWFORD. That is correct.

Mr. STUPAK. Have you ever done that? Not you, but FDA?

Mr. CRAWFORD. No. That's never been done. I assume that's because they have gotten the correction they sought.

Mr. STUPAK. Well, it's—I'm just concerned, it's a little bit like studies, you know, the FDA asks for studies and if they don't get the studies, they can always pull the drug from the market. And one of the hearings we had here earlier this year, when I asked Ms. Woodcock if that's ever been done, she said no. I'm concerned that the enforcement of the FDA in cases like this is always after the fact, and then it's not very vigorous, even when it is.

I'm trying to find what parameters or what criteria would you use where you'd actually step in. I still am bemused by the fact that the FDA is probably the only regulatory agency we have in the Federal Government that doesn't have subpoena power to get the studies that manufacturers do, but never submit to you, or if you ask for further raw data in support of the study submitted, you don't get it, in Serzone and a couple of other drugs that I know of.

So I'm a little suspicious, or I shouldn't say suspicious, but really don't believe the FDA does much in light of enforcement in these areas. So I'm trying to find out what criteria would you use before you begin some type of enforcement, other than they didn't follow through on the cease and desist order.

Mr. CRAWFORD. Yes. What I described is a chain of events where we would be seeking correction of a firm's course and if we didn't get that, then we would go as far as we needed to go in order to try to get the correction. Firms generally will—you know, acquiesce to what FDA's requests are at some point. Sometimes it takes quite a bit of coercion.

Mr. STUPAK. Sure. I realize you're fairly new to the FDA, and I think you're saying last night you've been there three or four times, and then out of the FDA, right?

Mr. CRAWFORD. Right. Yes, sir.

Mr. STUPAK. Do you believe the FDA should have subpoena power to be able to obtain studies and raw data from these drug manufacturers if there's a question as to the validity of a study?

Mr. CRAWFORD. Let me check if we've asked for that. We apparently have not sought that, at least recently. And one of the reasons is that we do have authority to require this information. And if they do not submit the information, then we can suspend the review of the product. And if it is a product that's already on the market, we can suspend the marketing of that product.

Mr. STUPAK. Sure. But the FDA has never done it. That's my point. Counsel's wrinkling their nose back there. If you know of some drug, you have actually pulled it because of that, I'd really like to know because they didn't submit it. Take Serzone, take Accutane. I can go down a couple of more if you want.

Mr. CRAWFORD. What we'll do is do a review of that and submit for the record if we ever have and then if we have, which ones we have.

Mr. STUPAK. Sure. I'd like to see that. I think the answer is no, but if you have any. Mr. Chairman with that I'd yield back. Thank you.

[The following was received for the record:]

CBER has revoked approved license applications when it subsequently discovered that the original applications contained false or misleading information. For example, the establishment and product licenses issued to Sclavo, S.p.A. (U.S. license 0238), were revoked after an inspection identified significant differences between the manufacturing methods used to manufacture product and those described in the license application. The product licenses revoked included Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, Tuberculin Purified Protein Derivative and Cholera Vaccine. See 58 Fed. Reg. 66,380 (December 20, 1993). CBER has also accepted the withdrawal of pending applications once substantive review has been deferred due to the presence of untrue statements in the application. For example, CBER accepted the withdrawal of pending license applications for two monoclonal antibody products.

FDA has repeatedly taken action to withdraw approval of new drug applications (NDAs), abbreviated applications (ANDAs), abbreviated antibiotic drug applications (AADAs), and new animal drug applications (NADAs) where sponsors failed to provide complete and truthful information to the Agency before or after marketing approval. In 1976, FDA initiated an action to withdraw approval of NDA 17-581 for Naprosyn (naproxen) Tablets on the ground that the sponsor had misstated or omitted material facts from the application. Specifically, FDA found that, because of such misstatements and omissions, a study report submitted as part of the NDA was "uninterpretable in documenting the lack of chronic toxic effects or carcinogenic potential of the drug." FDA found that the untrue statements "vitiate[d] the earlier conclusions reached by the Agency regarding long term safety of Naprosyn. *See* FDA, Naprosyn Tablets: Opportunity for Hearing on Proposal To Withdraw Approval of New Drug Application, 41 Fed. Reg. 45,605 (October 15, 1976). Between 1989 and 1995, FDA initiated proceedings to withdraw approval of certain and AADAs after it discovered untrue statements in batch and stability test records and bioequivalence studies (see Enclosure B). FDA has also initiated proceedings to withdraw approval of many NDAs, AADAs, ANDAs, and NADAs on the ground that the sponsor had failed to submit required annual reports or periodic reports as required by FDA regulations. *See* 58 Fed. Reg. 25,653 (April 27, 1993) (3 NADAs); 58 Fed. Reg. 33,445 (June 17, 1993) (one NADA); 58 Fed. Reg. 34,814 (June 29, 1993) (24 NADAs); 61 Fed. Reg. 9,999 (March 12, 1996) (41 NDAs); 61 Fed. Reg. 10,768 (March 15, 1996) (3 AADAs, 14 ANDAs); 61 Fed. Reg. 59,100 (November 20, 1996) (1 NADA); 62 Fed. Reg. 37,063 (July 10, 1997) (4 NDAs); 63 Fed. Reg. 29,233 (May 28, 1998) (2 NADAs); and 65 Fed. Reg. 16,397 (March 28, 2000) (158 ANDAs).

ENCLOSURE B

ANDA 71-737; Triamterene/HCTZ Capsules; AADA 61-471; Tetracycline Hydrochloride 500 mg Capsules; AADA 62-159; Cephalexin 250 mg and 500 mg Capsules; AADA 62-227; Doxycycline Hyclate 100 mg Capsules; AADA 62-779; Cephalexin for Oral Suspension, 125 mg/5 mL; AADA 62-780; Doxycycline Hyclate 50 mg Capsules; AADA 62-781; Cephalexin for Oral Suspension, 250 mg/5 mL; AADA 62-813; Cephradine 250 mg and 500 mg Capsules; AADA 62-863; Cephalexin 250 mg, 500 mg, and 1,000 mg Tablets; AADA 62-910; Clindamycin HCI 75 mg and 150 mg Capsules; ANDA 71-360; Triamterene 75 mg/Hydrochlorothiazide 50 mg Tablets; ANDA 71-531; Indomethacin ER 75 mg Capsules; ANDA 71-564; Orphenadrine Compound Tablets, Single Strength; ANDA 71-565; Orphenadrine Compound Tablets, Double Strength; ANDA 71-684; Meclofenamate 100 mg Capsules; ANDA 71-710; Meclofenamate 50 mg Capsules; ANDA 71-711; Indomethacin 25 mg Capsules; ANDA 71-712; Indomethacin 50 mg Capsules; ANDA 71-832; Trimipramine 25 mg Capsules; ANDA 71-833; Trimipramine 50 mg Capsules; ANDA 71-834; Trimiprarnine 100 mg Capsules; ANDA 71-901; Baclofen 10 mg Tablets; ANDA 71-902; Baclofen 20 mg Tablets; ANDA 72-167; Desipramine Hydrochloride 10 mg Tablets; ANDA 72-179; Mefenamic Acid 250 mg Capsules; ANDA 72-254; Desipramine Hydrochloride 150 mg Tablets; ANDA 71-642; Orphengesic Tables (25 mg orphenadrine citrate, 770 mg aspirin, 60 mg caffeine); ANDA 71-643; Orphengesic Forte Tables (50 mg orphenadrine citrate, 770 mg aspirin, 60 mg caffeine); ANDA 72-337; Triarnterene 75 mg and HCTZ 50 mg Tablets; ANDA 71-845; Triamterene 50 mg and HCTZ 25 mg Capsules; AADA 62-779; Cephalexin for Oral Suspension 125 mg/5 mL; AADA 62-781; Cephalexin for Oral Suspension 250 mg/5 mL; AADA 62-813; Cephradine 250 mg and 500 mg Capsules; AADA 62-863; Cephalexin 250

mg, 500 mg, and 1,000 mg Tablets; ANDA 71-684; Meclofenamate 100 mg Capsules; ANDA 71-710; Meclofenamate 50 mg Capsules; ANDA 70-642; Diazepam 2 mg; ANDA 70-643; Diazepam 5 mg; ANDA 70-644; Diazepam 10 mg; ANDA 70-421; Verapamil Hydrochloride Tablets, 80 mg; ANDA 70-422; Verapamil Hydrochloride Tablets, 120 mg; ANDA 71-020; Disopyramide Phosphate Capsules, 100 mg; ANDA 71-021; Disopyramide Phosphate Capsules, 150 mg; ANDA 71-558; Perphenazine and Amitriptyline HCI Tablets, 4 mg/50 mg; ANDA 71-661; Oxazepam Capsules, 10 mg; ANDA 71-662; Oxazepam Capsules, 15 mg; ANDA 71-663; Oxazepam Capsules, 30 mg; ANDA 89-700; Perphenazine Tablets, 8 mg; ANDA 70-400; Meclofenamate sodium 50 mg capsules; ANDA 70-401; Meclofenamate sodium 100 mg capsules; ANDA 88-711; Phenytoin sodium extended release capsules 100 mg; ANDA 62-392; Doxycycline hyclate tablets 100 mg; ANDA 88-207; Ergoloid mesylates tablets 1.0 mg; ANDA 70-727; Lorazepam Tablets, 0.5 milligram (mg); ANDA 70-728; Lorazepam Tablets, 1 mg; ANDA 70-729; Lorazepam Tablets, 2 mg; ANDA 70-881; Clonidine Hydrochloride Tablets, 0.1 mg; ANDA 70-882; Clonidine Hydrochloride Tablets, 0.2 mg; ANDA 70-883; Clonidine Hydrochloride Tablets, 0.3 mg; ANDA 89-387; Prednisone Tablets, 5 mg; ANDA 89-388; Prednisone Tablets, 10 mg; ANDA 89-389; Prednisone Tablets, 20 mg; ANDA 62-047; Erythromycin ethylsuccinate oral suspension, 200 and 400 mg; ANDA 71-929; Disopyramide phosphate extended release capsules, 100 mg; AADA 86-538; Nitroglycerin extended release capsules, 2.5 mg.

See 54 Fed. Reg. 35,535 (August 29, 1989); 54 Fed. Reg. 40,740 (October 3, 1989); 54 Fed. Reg. 42,367 (October 16, 1989); 54 Fed. Reg. 48,026 (November 20, 1989); 55 Fed. Reg. 8,995; 55 Fed. Reg. 9,360 (March 13, 1990); 55 Fed. Reg. 21,103 (May 22, 1990); 55 Fed. Reg. 25,712 (June 22, 1990); 55 Fed. Reg. 46,245 (November 2, 1990); 55 Fed. Reg. 47,542 (November 14, 1990); 55 Fed. Reg. 47,919 (November 16, 1990); 56 Fed. Reg. 2,528 (January 23, 1991); 60 Fed. Reg. 32,982 (June 26, 1995).

Mr. GREENWOOD. The Chair thanks the gentleman. One final question and then we're going to break. Mr. Whitfield did you have questions?

Mr. WHITFIELD. Mr. Chairman, I just have one brief question. I was just curious. Of the applications that are submitted for accelerated approval or fast track designation, what percent of those meet the criteria would you say for fast track?

Mr. CRAWFORD. We will check that and provide it for the record. We believe it to be 60 to 80 percent of requests.

[The following was received for the record:]

Fast track programs are designed to facilitate the development and expedite the review of new drugs that intended to treat serious or life-threatening conditions and demonstrate the potential to address unmet medical needs. Fast track emphasizes the critical nature of close early communication between FDA and sponsors. Procedures such as pre-Investigational New Drug (IND) and end of Phase 1 meetings are methods used to improve the efficiency of pre-clinical and clinical development. The fast-track process focuses on efforts by FDA and sponsors to reach early agreement on the design of the major clinical efficacy studies that will be needed to support approval. Fast track policies are primarily designed to expedite drug development during the IND stage. Approval under subpart H (accelerated approval) (Title 21, *Code of Federal Regulations* Part 314, Subpart H) allows for marketing approval of an NDA based on an effect on a surrogate endpoint along with well-controlled post-marketing studies. A drug developed under fast track may also qualify for accelerated approval.

CDER has received 172 requests for fast track designation since it was implemented in 1998. One hundred seventeen fast-track designations were granted. Forty-three fast-track designations were denied. Twelve fast-track designations are still pending, Based on these statistics, 73 percent met the criteria for fast-track designation.

Since 1978, CBER has granted 51 requests for fast-track designation and has denied 38 requests. Two applications are still pending. Based on these statistics, 56 percent met the criteria for fast-track designation.

Mr. WHITFIELD. Okay. Mr. Chairman that's all that I wanted to ask. Thank you for being with us today, Dr. Crawford.

Mr. CRAWFORD. Thank you very much.

Mr. GREENWOOD. The Chair thanks the gentleman. And finally, thinking about the Erbitux case and this line of questioning that we've been engaged in with the pre-approval marketing and so forth, in general, I think what we're trying to resolve here is if you have a promising drug, of course you want to create interest in investors and want to attract capital so that you can develop the drug. And of course that can be utilized the way it should work and it can be misused so that you actually attract investment for a product that—whose potential you're exaggerating.

And so the—obviously we think that the FDA has a role here. But we also realize that if you look at the Erbitux case, a lot of the—what some have called hyping, a lot of the promotion of the drug and its potential benefits occurred even before the application was submitted to the FDA. So we have this whole other period of time in which I suppose there's nothing at all we can do except caveat emptor. The investors will have to make their own decisions based on the personnel of the company and so forth as to whether they're going to believe these claims. That's basically a statement. I don't know if you choose to respond.

Mr. CRAWFORD. I don't believe we have any authority with that.

Mr. GREENWOOD. Yeah. And we probably shouldn't. All right. Well we thank you for testifying. This committee will recess now until 1.

[Brief recess.]

Mr. GREENWOOD. The committee will come the order, and as we do so, I welcome our next panel. And I will introduce them. We have Dr.—or rather Robert Goldhammer, chairman of the board of ImClone Systems. Welcome. Good afternoon. I say to all of you I apologize for delay, and there will be more because we have votes before us yet.

Mr. Goldhammer is chairman of the board of ImClone Systems. Paul Kopperl is a member of the board of directors of ImClone Systems. Welcome, sir. John Mendelsohn is the member of the board of directors also. Good to have you with us, Dr. Mendelsohn. Harlan Waksal, Dr. Waksal, good to have you back. Thank you for coming again. John Landes is the senior vice president for legal at ImClone Systems. Welcome, sir. And Katherine Vaczy, am I pronouncing that correct? Vaczy, vice president of the legal department at ImClone Systems.

We thank all of you for being here. You probably have been informed by our staff that this is an investigative hearing, and when we hold investigative hearings, it is our practice to take testimony under oath. And I would ask if any of you have any objections to providing your testimony under oath?

Seeing no such objections, I then advise you that pursuant to the rules of this committee and the rules of the House of Representatives, that you are each entitled to be represented by counsel, and let me start with Mr. Goldhammer, are you represented by counsel today, sir?

Mr. GOLDHAMMER. Yes.

Mr. GREENWOOD. Would you pull your microphone right up close to your mouth and make sure the button is on. It is flexible so you can—you can bend it up toward you so you don't have to bend

down. Now push the button again. Try it again. It still isn't on. All right. We'll get somebody to help you there.

Mr. GOLDHAMMER. Oh, wrong button.

Mr. GREENWOOD. Do whatever Dr. Waksal does. He has been here before.

If you would identify your counsel.

Mr. GOLDHAMMER. Yes. Charles Cobb.

Mr. GREENWOOD. Very well. Mr. Cobb, good to have you with us. Mr. Kopperl, are you advised by counsel as well?

Mr. KOPPERL. Yes, sir. It's Mr. Cobb.

Mr. GREENWOOD. Oh, same person. And Dr. Mendelsohn.

Mr. MENDELSOHN. Same person.

Mr. GREENWOOD. Dr. Waksal.

Dr. WAKSAL. Chip Lowenson.

Mr. GREENWOOD. Chip, would you identify yourself. Okay. Very good.

Mr. Landes.

Mr. LANDES. Yes. David Meister.

Mr. GREENWOOD. Who is there. Okay. And Ms. Vaczy.

Ms. VACZY. Eric Heikel.

Mr. GREENWOOD. Who is there. Very well.

In that case, if you would stand and raise your right hand, I'll administer the oath.

[Witnesses sworn.]

Mr. GREENWOOD. You are under oath, and we will—Okay. Mr. Goldhammer, do you have an opening statement that you'd like to make?

Mr. GOLDHAMMER. I do, sir.

Mr. GREENWOOD. Okay. Then please do. You're recognized for 5 minutes, and, again, if you would—if you can adjust that microphone so it is right where you want it.

TESTIMONY OF ROBERT F. GOLDHAMMER, CHAIRMAN OF THE BOARD, IMCLONE SYSTEMS, INC.; PAUL B. KOPPERL, MEMBER OF THE BOARD OF DIRECTORS, IMCLONE SYSTEMS, INC., JOHN MENDELSOHN, MEMBER OF THE BOARD OF DIRECTORS, IMCLONE SYSTEMS, INC.; AND HARLAN WAKSAL, CHIEF EXECUTIVE OFFICER, IMCLONE SYSTEMS, INC., ACCOMPANIED BY JOHN LANDES, SENIOR VICE PRESIDENT, LEGAL, IMCLONE SYSTEMS, INC., AND CATHERINE VACZY, VICE PRESIDENT, LEGAL, IMCLONE SYSTEMS, INC.

Mr. GOLDHAMMER. Thank you. Mr. Chairman and members of the subcommittee, good afternoon. My name is Robert Goldhammer. I joined ImClone Systems board of directors in October 1984, and I've been chairman since February 1991. Over the past 18 years, I've been privileged to witness the dramatic growth of a small startup company to the viable company ImClone represents today. The company was founded by Dr. Samuel Waksal and his brother Dr. Harlan Waksal in the early 1980's.

For the first 5 years the company sought to find its niche in establishing an appropriate scientific and business model for the company. To build ImClone, the Waksals assembled a distinguished scientific advisory board, and with the help of that board, the company began to focus on the treatment of cancers. In 1991, the com-

pany went to the public market on the basis of its potential as a young innovative biotechnology company with some promise.

A little more than a year ago, the company stood on the verge of a breakthrough. It had negotiated a strategic alliance with the Bristol-Myers Squibb Company that would facilitate its ability to bring hope in the form of Erbitux to hundreds of thousands of cancer patients. And it was in the process of seeking approval of Erbitux from the FDA.

While the subcommittee's primary interest is in that approval process, no doubt some of your questions today will center around ImClone's former president and CEO, Sam Waksal.

Let me say two things about this subject, if I might. First, despite the misconduct that has come to light, Sam Waksal was indispensable to this company, and an integral part of its success over those years. Sam Waksal was the one who recognized the potential of Erbitux early on, and it was he who was instrumental in building ImClone and in creating significant value for its shareholders and patients over a long period of time.

Second, as soon as allegations of wrongdoing by Sam Waksal began to surface in early 2002, the company's board acted quickly to address most of these issues.

We put in process a place to have outside legal counsel investigate the allegations of misconduct and report back to it. We debated the issues surrounding Sam Waksal vigorously, decided to about after, not before, a thorough investigation had taken place.

Today, despite the challenges of these recent months, ImClone remains a vibrant company that is working with its partners to give people hope and save lives.

We continue to believe that Erbitux will become an important treatment for cancer patients, and the company has an exciting pipeline of other products showing significant promise.

This board has met literally dozens of times this year in an effort to make sure that we in the company's management team are doing all we can and should be doing to get through these difficult times. Paul Kopperl on my left, the chairman of ImClone's audit committee, will discuss some of the significant governance changes the board initiated over the past 9 months.

Importantly, shortly after receiving the refusal to file letter from the FDA at the end of 2001, we quickly formed a committee of outside directors and retained legal counsel to address the serious issues facing the company. Above all, we have not led all of this controversy surrounding Sam Waksal to deflect any focus from our mission to get Erbitux back on track.

Dr. John Mendelsohn, a fellow board member and coinventor of Erbitux, will speak to it in more detail talking about this important drug.

Thank you for the opportunity to be here today. I'd be pleased to answer questions you may have. Thank you.

[The prepared statement of Robert F. Goldhammer follows:]

PREPARED STATEMENT OF ROBERT F. GOLDHAMMER, CHAIRMAN OF THE BOARD, IMCLONE SYSTEMS, INC.

Mr. Chairman and members of the Subcommittee, good afternoon.

My name is Robert Goldhammer. I joined the ImClone Systems Board of Directors in October 1984 and have been Chairman since February 1991.

Over the past eighteen years, I have been privileged to witness the dramatic growth of a small start-up to the viable company ImClone represents today.

The Company was founded by Dr. Samuel Waksal and his brother, Dr. Harlan Waksal, in the early 1980s. For the first five years, the Company sought to find its niche in establishing an appropriate scientific and business model.

To build the Company, the Waksals assembled a distinguished Scientific Advisory Board, and with the help of that board, the Company began to focus on the treatment of cancer. In 1991, the Company went to the public market on the basis of its potential as a young, innovative scientific biotechnology company with great promise.

A little more than a year ago, the Company stood on the verge of a breakthrough. It had negotiated a strategic alliance with Bristol-Myers Squibb Company that would facilitate its ability to bring hope in the form of Erbitux to hundreds of thousands of cancer patients. And it was in the process of seeking approval of Erbitux from the FDA.

While the Subcommittee's primary interest is in that approval process, no doubt some of your questions today will center around ImClone's former President and CEO, Sam Waksal.

Let me say two things about this subject. First, despite the misconduct that has come to light, Sam Waksal was indispensable to this Company and an integral part of its success over the years. Sam Waksal was the one who recognized the potential of Erbitux, and it was he who was instrumental in building ImClone and in creating significant value for its shareholders and patients over the long term.

Second, as soon as allegations of wrongdoing by Sam Waksal began to surface in early 2002, the Company's Board acted quickly to address these issues. We put a process in place to have its outside legal counsel investigate the allegations of misconduct and report back to it. We debated the issues surrounding Sam Waksal vigorously, and decided to act after, not before, a thorough investigation had taken place.

Today, despite the challenges of these recent months, ImClone remains a vibrant company that is working with its partners to give people hope and save lives. We continue to believe that Erbitux will become an important treatment for cancer patients, and the Company has an exciting pipeline of other products showing significant promise.

This Board has met literally dozens of times this year in an effort to make sure that we and the Company's management team are doing all we can and should be doing to get through these difficult times.

Paul Kopperl, Chairman of ImClone's Audit Committee, will discuss some of the significant corporate governance changes the Board initiated over the past nine months. Importantly, shortly after receiving the refusal-to-file letter from the FDA at the end of 2001, we quickly formed a committee of outside directors and retained separate legal counsel to address the serious issues facing the Company.

Above all, we have not allowed all of the controversy surrounding Sam Waksal to deflect focus from our mission to get Erbitux back on track. Dr. John Mendelsohn, a fellow Board member and a co-inventor of Erbitux, will speak to you in more detail concerning this important drug.

Thank you for the opportunity to be here today. I will be pleased to answer any questions you may have for me.

Mr. GREENWOOD. We thank you, Mr. Goldhammer.

Mr. Kopperl, do you have an opening statement?

Mr. KOPPERL. I do, sir.

Mr. GREENWOOD. Please proceed.

TESTIMONY OF PAUL B. KOPPERL

Mr. KOPPERL. Good afternoon. My name is Paul Kopperl. I chair the audit committee of ImClone Systems board of directors. On a personal note, Mr. Chairman, I'd like you and the committee to be aware that I have had my own personal battle with cancer, which is why I regard the success of Erbitux and the company as a critically important mission.

Since joining ImClone's board in December 1993, I have sought to ensure that the company has had sound corporate governance, policies in place and functioning. Over the years, we have reevalu-

ated these policies and improved them when and if appropriate. The goal was and is to have them be current best practices.

Let me mention some recent examples. In the fall of 2001, the audit committee reviewed the composition of the board's executive committee and recommended that it be comprised of a majority of outside directors. Accordingly, in November 2001, the board added two additional—two outside directors to our executive committee.

In addition, during this year, the board has rigorously reviewed many of its previous corporate governance policies and implemented new ones where we thought improvements could be made. Although I do not have sufficient time to describe them in detail this afternoon, I would like to present you with a brief overview, if I may, of the significant steps that the board has taken to improve corporate governance at ImClone.

In April of this year, the board adopted new enhancements to its securities law compliance and insider trading policies. As a result, the company now has 16 officers who must file reports of their transaction under section 16 of the Securities and Exchange Act.

The board has also put in place a strict process to be followed before the company may enter into any related party transactions, and in an abundance of caution and even to avoid any appearance of impropriety, we terminated the consulting agreements between the company and two of the scientific members of the board. And these were the only directors with such consulting contracts.

But we didn't stop there. The company recently hired a highly qualified full-time vice president to perform an internal audit function reporting directly to the audit committee.

Finally, the full board at our next meeting in November will be acting on a recommendation by one of our board committees to adopt a code of conduct for the entire board, a code of conduct for officers and employees and specific charters for those board committees, such as the compensation committee that do not now have it.

As Mr. Goldhammer explained, when the board learned of allegations of wrongdoing by the company's then-chief executive officer Sam Waksal, the board took these allegations very seriously and took appropriate action.

After a deliberate and thorough process, including investigations by outside counsel and a careful weighing of the relevant facts as we knew them, the board concluded in May 2002 that it was in the best interest of the company for Sam Waksal to step down. On May 22, 2002, he did resign.

In August, the company filed a lawsuit against Sam Waksal to recover the money paid him in his separation agreement, because we believe he failed to cooperate with Federal investigations into his conduct. In this regard, it should be emphasized that as you know, no company policy, however strong, can prevent an officer or other employee from engaging in personal wrongdoing if that person chooses to evade company rules and engage in wrongful and perhaps illegal behavior.

In closing, let me say that this board has faith in Erbitux and faith in ImClone. That faith, Mr. Chairman, is why each of us continues to serve and why we continue to maintain substantial holdings of its common stock. The goal of this board has been, and re-

mains to guide ImClone into the future and ensure that we continue to fulfill our duties to the company's shareholders, to the patients afflicted by this dread disease and to the public. And I thank you for this opportunity.

[The prepared statement of Paul B. Kopperl follows:]

PREPARED STATEMENT OF PAUL B. KOPPERL, CHAIR, AUDIT COMMITTEE, IMCLONE SYSTEMS, INC.

Good afternoon. My name is Paul Kopperl. I chair the Audit Committee of ImClone Systems' Board of Directors. I also wish to mention, Mr. Chairman, that I have had my own personal battle with cancer—which is why I regard the success of Erbitux and the Company as a personal mission.

Since joining ImClone's Board in December 1993, I have sought to ensure that the Company had sound corporate governance policies in place and functioning. Over the years, we have reevaluated these policies so that they remained current best practices.

Let me mention some recent examples: In the Fall of 2001, the Audit Committee reviewed the composition of the Board's Executive Committee and recommended that it be comprised of a majority of outside directors. Accordingly, in November 2001, the Board added two additional outside directors to the Executive Committee.

In addition, during this year, the Board has rigorously reviewed many of its previous corporate governance policies and implemented new ones where we thought improvements could be made. Although I do not have sufficient time to describe them all in detail to you now, I would like to present with you a brief overview of the significant steps the Board has taken to improve corporate governance at ImClone.

In April of this year, the Board adopted new enhancements to its securities laws compliance and insider trading policies. As a result, the Company now has 16 officers who must file reports of their transactions under section 16 of the Securities and Exchange Act. The Board has also put in place a strict process to be followed before the Company may enter into any related-party transaction. And in an abundance of caution, and to avoid even any appearance of impropriety, we terminated the consulting agreements between the Company and the three scientific members of the Board of Directors.

But we didn't stop there. The Company recently hired a highly qualified full-time Vice-President to perform an internal audit function reporting to the Audit Committee. Finally, the full Board will soon be acting on a recommendation by one of the Board committees to adopt a code of conduct for the Board, a code of conduct for officers and employees, and specific charters for those Board committees that do not currently have them.

As Mr. Goldhammer explained, when the Board learned of allegations of wrongdoing by the Company's then-CEO, Sam Waksal, the Board took them seriously and took appropriate action. After a deliberate and thorough process, including investigations by outside counsel, and a careful weighing of the relevant facts, as we knew them, the Board concluded in May 2002 that it was in the best interest of the Company for Sam Waksal to step down. On May 22, 2002, he resigned. In August, the Company filed a lawsuit against him to recover the money paid him in his separation agreement because we believe he breached that agreement by failing to cooperate with federal investigations into his conduct. In this regard, it bears mention that no Company policy—however strong—can prevent an officer or other employee from engaging in personal wrongdoing if that person chooses to evade company rules and engage in wrongful, and perhaps illegal behavior.

In closing, let me say that this Board has faith in Erbitux and faith in ImClone. We are bullish on the company, which is why each of us continues to serve and maintain substantial holdings in its stock.

The goal of this Board has been and remains to guide ImClone into the future and ensure that we continue to fulfill our duties to the Company's shareholders, to the patients afflicted by this dread disease, and to the public. Thank you.

Mr. GREENWOOD. We thank you, Mr. Kopperl.

And let me add, if I may, that it is because this committee is so intent on seeing that Erbitux, if it does have the potential that many believe it does, is approved and that we have an expeditious means of getting all innovative cancer products approved so that

they can get to the patients, that is our objective. That is our goal, and that's what this is all about.

Thank you, sir.

Dr. Mendelsohn, you're recognized for your opening statement.

TESTIMONY OF JOHN MENDELSOHN

Mr. MENDELSOHN. Thank you. Good afternoon, Mr. Chairman, and members of the subcommittee. My name is John Mendelsohn, and I'm here today as a member of the board of directors of ImClone Systems, Incorporated. I am currently the President of and a professor at the M.D. Anderson Cancer Center at the University of Texas. I have also had leadership roles in the Department of Medicine at Memorial Sloan-Kettering Cancer Center, and the University of California, San Diego.

For more than 30 years, I have worked at these institutions to create and expand cancer programs that have made important contributions to the Nation's efforts to understand and conquer cancer, and for 30 years, I served as principal investigator in laboratory research at these institutions studying the regulation of cell growth.

Cells have a molecular engine that doesn't run until you turn it on by putting a key, a growth factor molecule, into the ignition, a growth factor receptor on the cell surface.

In the early 1980's, I working with collaborators, produced monoclonal antibody 225, now known as Erbitux. Our research was built on the then-novel concept that by targeting especially terminal growth factor receptors, we could inhibit a tumor's growth by blocking a molecular signalling pathway.

Today, this concept is well accepted and is the basis for Herceptin and Iressa, in addition to Erbitux.

In 1992, I was asked to join ImClone's scientific advisory board to consult with the company on a regular basis about the scientific basis behind monoclonal antibody C225 and worked with ImClone to help move the drug through the clinical trial process. In 1998, I joined ImClone's board of directors.

As someone who has devoted his life to cancer research, I can't stress enough just how critical ImClone has been to the development of this revolutionary cancer drug. Until ImClone licensed C225 in 1993, no other company had taken a serious interest in developing this treatment. Sam Waksal was one of the few scientists who not only understood the molecular basis of treatment with C225, but developed and executed a plan to transform it from a molecule in the lab into a powerful and innovative cancer treatment. Under Sam Waksal's leadership, ImClone raised money for the drug's research and development, guided the drug through completion of phase II studies of its efficacy and made it the centerpiece of a major collaboration with one of the word's leading pharmaceutical companies.

Sam Waksal's personal failures should not detract from what is really important, that Erbitux shows great promise. Although questions rightfully abound about why the FDA did not accept the Erbitux BLA for filing, each study that has been conducted strongly suggests that Erbitux is an active anticancer agent in end-stage colon cancer.

As the subcommittee may know, the vast majority of patients diagnosed with colorectal cancer are resistant to chemotherapy. Our laboratory research shows that Erbitux, when used in combination with other agents, represents a promising treatment to help overcome this resistance in order to shrink tumors and perhaps extend life.

The 9923 study was specifically designed to test this important hypothesis. The accelerated approval process which Congress enacted was designed to make certain that drugs which address an unmet medical need in a devastating disease can become available to patients more rapidly based on the results of a phase II study. The question posed in a phase II trial is whether of new drug is worthy of further development. The Erbitux phase II trials had positive results.

I am disappointed that Erbitux will not be available for patients who need it as soon as we had originally hoped.

I joined and continue to work with ImClone, because I believe its scientists have the vision, the desire and the capability to get this new treatment to patients.

My personal goal remains to do everything in my power to bring Erbitux through the approval process and to patients with cancer.

Thank you very much.

[The prepared statement of John Mendelsohn follows:]

PREPARED STATEMENT OF JOHN MENDELSOHN, BOARD OF DIRECTORS, IMCLONE SYSTEMS, INC.

My name is John Mendelsohn and I am here today as a member of the Board of Directors of ImClone Systems Incorporated.

I am currently the president of, and a professor at, the MD Anderson Cancer Center at the University of Texas. I have also had leadership roles in the Department of Medicine at Memorial Sloan-Kettering Cancer Center and the University of California, San Diego. For more than 30 years, I have worked at these institutions to create and expand cancer programs that have made important contributions to the nation's efforts to understand and conquer cancer. And for 30 years I served as principal investigator in laboratory research at these institutions studying the regulation of cell growth.

Cells have a molecular engine that doesn't run until you turn it on by putting a key (a Growth Factor molecule) into the ignition (a Growth Factor receptor on the cell surface). In the early 1980s, I, working with collaborators, produced monoclonal antibody 225, now known as Erbitux. Our research was built on the then novel concept that by targeting Epidermal Growth Factor receptors, we could inhibit a tumor's growth by blocking a molecular signaling pathway. Today, this concept is well accepted and is the basis for Herceptin and Iressa, in addition to Erbitux.

In 1992, I was asked to join ImClone's Scientific Advisory Board to consult with the company on a regular basis about the scientific basis behind monoclonal antibody C225, and worked with ImClone to help move the drug through the clinical trial process. In 1998, I joined ImClone's Board of Directors.

As someone who has devoted his life to cancer research, I can't stress enough just how critical ImClone has been to the development of this revolutionary cancer drug.

Until ImClone licensed C225 in 1993, no other company had taken a serious interest in developing this treatment. Sam Waksal was one of the few scientists who not only understood the molecular basis of treatment with C225, but developed and executed a plan to transform it from a molecule in the lab into a powerful and innovative cancer treatment. Under Sam Waksal's leadership, ImClone raised money for the drug's research and development, guided the drug through completion of Phase II studies of its efficacy, and made it the centerpiece of a major collaboration with one of world's leading pharmaceutical companies.

Sam Waksal's personal failings should not detract from what is really important—that Erbitux shows great promise. Although questions rightfully abound about why the FDA did not accept the Erbitux BLA for filing, each study that has been con-

ducted strongly suggests that Erbitux is an active anti-cancer agent in end stage colon cancer.

As the Subcommittee may know, the vast majority of patients diagnosed with colorectal cancer are resistant to chemotherapy. Our laboratory research shows that Erbitux, when used in combination with other agents, represents a promising treatment to help overcome this resistance in order to shrink tumors, and perhaps extend life. The 9923 study was specifically designed to test this important hypothesis.

The accelerated approval process, which Congress enacted, was designed to make certain that drugs which address an unmet medical need in a devastating disease can become available to patients more rapidly based on the results of a Phase II study. The question posed in a Phase II trial is whether a new drug is worthy of further development. The Erbitux Phase II trials had positive results.

I am disappointed that Erbitux will not be available for patients who need it as soon as we had originally hoped. I joined and continue to work with ImClone because I believe its scientists have the vision, the desire and the capability to get this new treatment to patients. My personal goal remains to do everything in my power to bring Erbitux through the approval process and to patients with cancer. Thank you.

Mr. GREENWOOD. Thank you. And, again, we wish you success with them.

Dr. Waksal.

TESTIMONY OF HARLAN WAKSAL

Mr. WAKSAL. Mr. Chairman, and members of the subcommittee, I am Harlan Waksal. I am the chief executive officer and president of ImClone Systems. I became the CEO of ImClone just over a hundred days ago. This has been a challenging time for the company, and I've worked hard, everyone, everyone at the company has worked hard to keep focused on the most important objective, bringing to market a promising new anticancer drug, Erbitux.

Independent clinical studies performed at the Nation's finest medical institutions demonstrated that Erbitux holds promise for treating patients with advanced cancer.

Shortly after I became CEO, ImClone's cofounder, my brother Sam, was arrested and charged with a number of offenses. Our company is fully cooperating with investigations being conducted by a variety of investigative bodies and agencies. Yet even as we deal with these challenges, we've turned a new page. I am here to report today that we have made progress on a number of fronts. So let me review briefly our efforts on three vital areas: Corporate governance, management reform and clinical testing.

First corporate governance. ImClone has put in place procedures that comply with the recently enacted Sarbanes-Oxley law. We put in place new measures that will strengthen further our existing internal controls. We have, No. 1, enacted a new rigorous insider trading policy. No. 2, greatly increased the number of officers who are required to file reports about their securities trading. And No. 3, ended all consulting arrangements with directors.

In short, we are moving forward in a way that should rebuild the confidence of investors, regulators, the oncology community and the public.

Second, management reform. While I take pride in our company's achievements in its early years, we have made some changes in the past hundred days to reflect our company's new direction. Although the legal staff has served us well in the past, even before I became CEO, we set in motion the strengthening of the Office of the General Counsel. I am working closely with our new chief legal counsel

as we adapt our controls as the company grows. We have also created a new position, vice president for internal audit. We recently hired a highly qualified individual to serve in this important role.

In addition, we've added experienced and depth to the regulatory and clinical affairs departments. We are working closer than ever with our experienced partners at Bristol-Myers Squibb and with America KGAA from Germany to gain the benefit of their expertise and resources.

Third, clinical testing. Erbitux is currently being tested in several clinical trials around the country and around the world. Based on the regulatory approach we have developed with our partners and continue to discuss with the FDA, we are moving forward with our clinical development plans. In connection with these plans—with this program that we've put in place, we plan to treat several thousand patients in various clinical trials of Erbitux in a number of different cancer types.

And finally, as part of our colorectal clinical development program, we will be reinitiating a compassionate use program for colorectal cancer patients who do not qualify for those other clinical trials that are being put in place.

The broad scope of our clinical development plans confirms our success in manufacturing Erbitux for use in clinical trials, our commitment to cancer patients and our belief and our partner's belief in this drug. And beyond Erbitux, we have a number of other drugs in our development pipeline.

ImClone's immediate mission is clear, to gain regulatory approval for and bring to market a promising new anticancer drug, Erbitux.

Our company is working hard to put the controversies of the past behind us and to focus our time, our energy and resources on the task at hand, helping patients who otherwise have little hope.

I look forward to answering any questions you have today, sir.

[The prepared statement of Harlan Waksal follows:]

PREPARED STATEMENT OF HARLAN WAKSAL, CEO, IMCLONE SYSTEMS INCORPORATED

Mr. Chairman and Members of the Subcommittee, I am Harlan Waksal. I am the Chief Executive Officer and President of ImClone Systems Incorporated.

I became CEO of ImClone just over 100 days ago. This has been a challenging time for ImClone. I have worked hard—everyone at the company has worked hard—to keep focused on our most important objective: bringing to market a promising new anti-cancer drug, Erbitux. Independent clinical studies performed at the nation's finest medical institutions demonstrate that Erbitux holds promise for treating patients with advanced cancer.

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We have also created a new position—Vice President for Internal Audit. We recently hired a highly qualified individual to serve in this important role. In addition, we have added experience and depth to our regulatory and clinical affairs departments. We are also working closer than ever with our experienced partners at Bristol-Myers Squibb and Merck KGAA to gain the benefit of their expertise and resources.

Third, clinical testing. Erbitux is currently being tested in several clinical trials around the country and around the world. Based on the regulatory approach that we developed with our partners and continue to discuss with the FDA, we are moving forward with our clinical development program for Erbitux. In connection with this program, we plan to treat several thousand patients in various clinical trials of Erbitux in a number of different cancer types.

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ImClone's immediate mission is clear: to gain regulatory approval for, and bring to market, a promising cancer drug, Erbitux. Our company is working hard to put the controversies of the past behind us, and to focus our time, energy, and resources on the task at hand: helping patients who otherwise have little hope.

Mr. GREENWOOD. Thank you, Dr. Waksal.

Mr. Landes.

TESTIMONY OF JOHN B. LANDES

Mr. LANDES. Thank you, Chairman Greenwood, and members of the subcommittee. My name is John Landes. I have worked for ImClone Systems for more than 18 years. For most of that time, I was general counsel and corporate secretary. As general counsel, I was head of the company's legal department. I also worked several years in the area of business development. I joined ImClone in its beginning in 1984. During my time at ImClone, I have watched it grow from a three-person research organization into a cutting-edge biotechnology company. For its first 7 years, ImClone was a privately owned business. It became a publicly traded company in 1991. It has grown from 3 employees to approximately 400. Most of whom are scientists.

The role of my department is to handle legal matters for all operating units of the company. While ImClone grew, its need for legal advice constantly evolved. As a result, my department has had to keep abreast of a variety of legal issues facing the company, from real estate to technology transfer, to employment, for example.

At each step along the way, under my supervision, our small department has worked very hard to provide management with accurate and well-grounded legal advice and service as the company has pursued its goal of producing a pipeline of therapeutic products for patients with cancer.

Because we have always been a small health department, our lawyers have worked closely with and relied upon several respected outside law firms to assist us with matters requiring particular expertise, such as security law matters, drawing upon specialists at

outside law firms is a common practice, among in-house counsel, and it has been very useful to those of us at ImClone.

Although the people in my department are not scientists, our overriding goal is to help ImClone develop treatments for cancer. As one of its original employees, I am very proud of what ImClone has accomplished. I remain committed to helping the company reach its goal. With that, I welcome the opportunity to answer any questions that you may have.

[The prepared statement of John B. Landes follows:]

PREPARED STATEMENT OF JOHN LANDES, SENIOR VICE PRESIDENT, LEGAL, IMCLONE SYSTEMS, INC.

Thank you Chairman Greenwood and members of the subcommittee.

My name is John Landes. I have worked for ImClone systems for more than 18 years. For most of that time, I was general counsel and corporate secretary. As general counsel, I was head of the company's legal department. I also worked several years in the area of business development.

I joined ImClone at its beginning, in 1984.

During my time at ImClone, I have watched it grow from a three-person research organization into a cutting-edge biotechnology company. For its first seven years, ImClone was a privately owned business. It became a publicly traded company in 1991. It has grown from three employees to approximately 400, most of whom are scientists.

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Because we have always been a small legal department, our lawyers have worked closely with—and relied upon—several respected outside law firms to assist us with matters requiring particular expertise, such as securities law matters. Drawing upon specialists at outside law firms is a common practice among in-house counsel, and it has been very useful to those of us at ImClone.

Although the people in my department are not scientists, our overriding goal is to help ImClone develop a treatment for cancer. As one of its original employees, I am very proud of what ImClone has accomplished. I remain committed to helping the company reach its goal.

With that, I welcome the opportunity to answer any questions you may have.

Mr. GREENWOOD. Thank you, Mr. Landes.

Ms. Vaczy.

TESTIMONY OF CATHERINE VACZY

Ms. VACZY. Good afternoon, Mr. Chairman, members of the subcommittee. My name is Catherine Vaczy. I'm the vice president legal and associate general counsel of ImClone Systems, Incorporated.

Much has been said about our small company over the last several months, and I am pleased to be here today to tell you about ImClone Systems from my perspective. I came to ImClone in 1997 as the second attorney in the ImClone legal department which today employs six lawyers. I hope that working in a biotechnology company would offer me a more intimate and satisfying experience than being on the outside looking in as I had done for several years as an associate in the corporate law department of a law firm. ImClone did not disappoint me. I was quickly won over by the warmth of this small company, the important work it is pursuing and the stories of how it had persevered through hard times.

In 1999, we were encouraged in our work when the company's development staged anticancer therapeutic Erbitux showed promise in early stage clinical trials.

Continuing the development process to hopefully make Erbitux available to cancer patients became the priority of our small company, but to do this, we had to grow and grow dramatically. The number of employees at ImClone nearly doubled on an annual basis in each of the next 3 years. This tremendous growth offered a whole host of difficult challenges that were as basic as where to put all of these people and as complex as how to adapt our policies, procedures and controls to this ever-changing landscape.

In addressing these challenges, I was heartened by the importance of our task and the competence, dedication and determination of my peers. I think that on a whole, we have succeeded very well. We constantly review all of our policies to try to ensure that they are as effective and efficient as possible. We consult with outside counsel and other advisers, and we belong to trade associations and attend conferences to stay abreast of changing laws and trends. We do this not because we have failed in the past, but because we want to be even better in everything we do.

Regarding trading company securities by officers and employees, we believe we have always had in place an appropriate insider trading policy. Throughout my time with the company, we repeatedly reviewed our insider trading policy with outside counsel at preeminent law firms advising us, and were always assured that the policy was appropriate.

We also repeatedly considered whether the number of our officers who filed in courts of their ImClone stock transactions with the FCC was appropriate, and we repeatedly reviewed that question explicitly with our outside counsel, again preeminent in this field.

And we were always assured, in no uncertain terms, that the determination was appropriate.

To conclude, I think it is important that everyone remember that ImClone is a real company with real people working hard to achieve real results. I am proud to be a part of this effort. Thank you.

[The prepared statement of Catherine Vaczy follows:]

PREPARED STATEMENT OF CATHERINE VACZY, VICE PRESIDENT, LEGAL AND ASSOCIATE GENERAL COUNSEL, IMCLONE SYSTEMS, INC.

Good afternoon, Mr. Chairman, members of the Subcommittee. My name is Catherine Vaczy. I am the Vice President, Legal and Associate General Counsel of ImClone Systems Incorporated. Much has been said about our small company over the last several months and I am pleased to be here today to tell you about ImClone Systems from my perspective.

I came to ImClone in 1997 as the second attorney in the ImClone Legal Department, which today employs six lawyers. I hoped that working in a biotechnology company would offer me a more intimate and satisfying experience than being on the outside looking in as I had done for several years as an associate in the corporate law department of a law firm.

ImClone did not disappoint me. I was quickly won over by the warmth of this small company, the important work it was pursuing and the stories of how it had persevered through hard times. In 1999, we were encouraged in our work when the Company's development stage anti-cancer therapeutic, ERBITUX, showed promise in early stage clinical trials. Continuing the development process to hopefully make Erbitux available to cancer patients became the priority of our small company. But to do this, we had to grow, and grow dramatically. The number of employees at ImClone nearly doubled on an annual basis in each of the next three years.

This tremendous growth offered a whole host of difficult challenges that were as basic as where to put all of these people and as complex as how to adapt our policies, procedures and controls to this ever changing landscape.

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To conclude, I think it is important that everyone remember that ImClone is a real company, with real people working to achieve real results. I am proud to be a part of this effort.

Thank you.

Mr. GREENWOOD. Thank you, Ms. Vaczy.

And the Chair recognizes himself for 10 minutes for questioning, and I'll start with you, Ms. Vaczy. You might want to bend that microphone and pull it over a little closer.

Before I do that, I would ask unanimous consent to place the document binder into the record. And without objection, it shall be done.

Ms. Vaczy, I'd like to ask you about an issuers letter requested by the Bank of America in January 2002 for warrants owned by Sam Waksal. First, so I'm clear, an issuer's letter is a request to a company to, in effect, certify that a person owns certain financial instruments in the company such as in this case warrants. Is that correct? Is that your understanding?

Ms. VACZY. Yes. It is a representation of the company, yes.

Mr. GREENWOOD. Okay. In January of this year, can you tell me why Bank of America came to you for an issuers letter related to Sam Waksal?

Ms. VACZY. You're referring to one that they requested from me as opposed to one that I—a copy of one that I received from them? Could I perhaps see the one that we're discussing?

Mr. GREENWOOD. It's Tab 26 in your binder there.

Ms. VACZY. Well, this doesn't appear to be an issuer's letter in Tab 26. It is a letter to Dr. Waksal, Sam Waksal and Dr. Harlan Waksal.

I'm familiar with an issuers letter. This does not appear——

Mr. GREENWOOD. All right. We'll try to correct that. But the question is—well, let me ask you this. Did Bank of America this January ask you for an issuers letter, or did you have discussion with a bank about an issuer's letter to certify that it had something to do with Mr. Waksal?

Ms. VACZY. Yes. I did.

Mr. GREENWOOD. Why don't you tell us what that was.

Ms. VACZY. I had discussions with counsel to Bank of America on Dr. Sam Waksal's behalf around the middle of January 2002.

Those discussions revolved around Dr. Sam Waksal moving a loan to Bank of America, that he had at another financial institution, and in connection with that, he was pledging securities of ImClone as collateral. And the bank was requesting an issuer's letter from the company to certify as to certain matters regarding a securities——

Mr. GREENWOOD. Okay. And did the Bank of America then give you or provide you the letter in Tab 26? Oh, wait a minute. I'm told the problem is that it's Tab 10.

Ms. VACZY. Yes, they did.

Mr. GREENWOOD. Okay. And what is the significance of this type of document?

Ms. VACZY. Of this particular document or in general?

Mr. GREENWOOD. Yes.

Ms. VACZY. In my conversations with Bank of America in January 2002 with the counsel to Bank of America, the counsel advised me of a warrant that had been pledged to them and sent to me this letter to demonstrate that they, in fact, had that pledge.

Mr. GREENWOOD. Mr. Landes, if you would take a look at that letter as well, and at the bottom of the document is a signature that reads John Landes. Is that your signature?

Mr. LANDES. No, it's not.

Mr. GREENWOOD. Okay. When did you first see the document with your forged signature on it?

Mr. LANDES. I saw this document on January 14, 2002.

Mr. GREENWOOD. Okay. You met with Sam Waksal about the document. Right?

Mr. LANDES. Yes, I did.

Mr. GREENWOOD. And did Sam Waksal deny that he signed your signature to that document?

Mr. LANDES. No, he did not.

Mr. GREENWOOD. Did you report this to the Federal authorities?

Mr. LANDES. No, I did not.

Mr. GREENWOOD. Was the board notified about the forgery to Bank of America?

Mr. LANDES. Yes, it was.

Mr. GREENWOOD. Okay. Let me then address some questions to the members of the board, Mr. Goldhammer, Mendelsohn and Kopperl. Were you aware of this letter?

Mr. KOPPERL. Yes.

Mr. GREENWOOD. And Mr. Goldhammer, when did you become aware of this allegation of forgery?

Mr. GOLDHAMMER. Early——

Mr. GREENWOOD. Take the microphone, please.

Mr. GOLDHAMMER. I'm sorry. The first part of February, I think.

Mr. GREENWOOD. Okay. And Mr. Kopperl.

Mr. KOPPERL. It was early February.

Mr. GREENWOOD. Dr. Mendelsohn.

Mr. MENDELSOHN. As I remember, it was in February.

Mr. GREENWOOD. Okay. Why wasn't Sam Waksal fired immediately?

Mr. GOLDHAMMER. All of the loans—the forgery issue—as soon as we found out about it, we immediately formed a special committee

of the board and hire outside counsel to investigate this allegation and do it as quickly as possible.

Mr. GREENWOOD. What did you learn from that investigation?

Mr. GOLDHAMMER. I'm sorry?

Mr. GREENWOOD. What did you learn from that investigation?

Mr. GOLDHAMMER. We never really learned in that—the investigation was not complete by the time Sam was asked to resign.

Mr. GREENWOOD. Okay. But you knew before you had initiated your investigation——

Mr. GOLDHAMMER. Yes.

Mr. GREENWOOD. [continuing] that Mr. Landes said this is not my signature, it's forged, and Mr. Waksal didn't deny that; is that correct?

Mr. GOLDHAMMER. Yes, sir.

Mr. GREENWOOD. Mr. Landes, let me go back to you. This wasn't the first time that Sam Waksal had forged your signature. Isn't that correct?

Mr. LANDES. There was a previous occasion that I was familiar with in which he had signed my name to a document.

Mr. GREENWOOD. Can you tell us about that? Is that the 1991 case where he signed for you and Harlan Waksal on a stock certificate? Listen.

Mr. LANDES. Yes. I learned in 1991 that in 1986 that Sam had attempted to convey some of his own shares through an ImClone stock certificate, shares that he owned, and this I learned in 1991 and did obtain a copy of the stock certificate.

Mr. GREENWOOD. The records show that Dr. Sam Waksal issued an ImClone stock certificate with those—these forged signatures and received payment for this of $90,000. Do you know what Sam Waksal did with the $90,000?

Mr. LANDES. No, I don't, Mr. Chairman.

Mr. GREENWOOD. When did you learn of this forgery?

Mr. LANDES. I learned of this in 1991.

Mr. GREENWOOD. Okay. And if you look at Tab 2, I think that will demonstrate your knowledge in 1991.

To whom did you report these acts of forgery by Sam Waksal, and when?

Mr. LANDES. Well, I immediately had a conversation with Sam, a number of conversations with him, to learn what the circumstances were, and what I learned was that Sam did not understand how one conveyed one's own shares. I told him that this was clearly not how one did this. So my discussions were——

Mr. GREENWOOD. So he thought that the appropriate way to do it was through forgery?

Mr. LANDES. No, Mr. Chairman. I think he did not—he did not recognize how shares were to be conveyed if you owned them, but I believed that he—this was a good-faith misunderstanding or lack of knowledge on his part which I just——

Mr. GREENWOOD. I'm trying to understand how one could have a lack of knowledge about a technical financial matter that would result in one's forging another person's name on a document.

Mr. LANDES. Mr. Chairman, we were a very small company at the time. We, in fact, were probably less than a year old, 1986, I think we were just beginning.

Mr. GREENWOOD. So when did you report that incident to the board of directors?

Mr. LANDES. At that time I did not report it to the board of directors, because as I say, my understanding was that this was really a misunderstanding on Sam's part which we discussed at length.

Mr. GREENWOOD. My children know better than that, Mr. Landes.

Did Sam ask you not to report it to anyone?

Mr. LANDES. No, he did not.

Mr. GREENWOOD. Okay. So you made that decision on your own?

Mr. LANDES. I did.

Mr. GREENWOOD. Okay. Let me return to the members of the board of directors. When did the board also learn that Sam Waksal had forged signatures on an ImClone stock certificate? Dr. Goldhammer—Mr. Goldhammer.

Mr. GOLDHAMMER. Just recently, a couple of weeks.

Mr. GREENWOOD. Just a couple weeks ago. Do you think that was a result of our investigation?

Mr. GOLDHAMMER. I don't know. I don't know.

Mr. GREENWOOD. How did you learn 2 weeks ago?

Mr. GOLDHAMMER. It came up in—March 21. March 21 is when we learned—when I learned.

Mr. GREENWOOD. Okay. Apart from these two forgeries, the board learned of certain other improprieties or questionable business practices by Sam Waksal, but similarly chose to look the other way. Please tell me if I'm incorrect in any respect. On February 22, 2002, the press reported that Sam Waksal had made illegal short-swing profits on ImClone stock and disgorged $486,000 to ImClone.

Did you see this article, and were you ever aware of these allegations before this article was published? Do you want to see the article? It's Tab 31.

Mr. GOLDHAMMER. Would you repeat the question, please? I think I should remember.

Mr. GREENWOOD. On February 22 of this year, the press reported that Sam Waksal had made illegal short-swing profits on ImClone stock and had disgorged $486,000 to ImClone. So the question is, were you aware of that in February of this year? Any of the members of the board recall learning about that when this was reported to the press in February?

Mr. KOPPERL. We did learn about it at approximately this time, Mr. Chairman, and we took appropriate action, which was to have, in the first instance, counsel investigate the relevant facts, and then the company demanded that Dr.—that Sam Waksal repay the short-term profits.

Mr. GREENWOOD. Okay. My time is rapidly expiring, but Dr. Waksal, when did you know about this—first learn about this 10-year-old forgery?

Mr. WAKSAL. You're talking about the stock certificate? I learned about 2 weeks ago.

Mr. GREENWOOD. Okay. Well, my time is expired. The Chair recognizes the gentleman from Florida to inquire for 10 minutes.

Mr. DEUTSCH. Thank you, Mr. Chairman. Mr. Kopperl, your testimony really begs the question, why have you been a member of the board since 1993, as in your words, sought to ensure that the

company has sound corporate governance policies in place and functioning, over the entire time were no such sound policies put in place until the scandal broke?

Mr. KOPPERL. I beg your pardon. I didn't catch the last part of that.

Mr. DEUTSCH. The policies that you articulated in your testimony, why were they just put into place only since the scandal broke? Why were those policies not in place previously?

Mr. KOPPERL. As the chairman of the audit committee, part of my responsibility was, as your question indicates, to make sure that ImClone had appropriate procedures in place. When I joined the board of directors, there were procedures in place, and in the main those procedures worked okay. We continually review them, and to the extent that we deemed that improvements could be made, we made improvements as the company continued to grow and evolve.

So there were governance policies in place about short-swing profits, about insider trading and so on.

Mr. DEUTSCH. Specifically you had a policy or you had an executive committee composed of Sam Waksal, Harlan Waksal and Bob Goldhammer. Was it a good policy to have only those individuals required to report stock transactions?

Mr. KOPPERL. To report stock transactions?

Mr. DEUTSCH. That's correct. That was your policy that only those three individuals had to report stock transactions.

Mr. KOPPERL. Plus the—plus all the directors, sir.

Mr. DEUTSCH. That's correct. But you've changed that policy now.

Mr. KOPPERL. We have changed the policy.

Mr. DEUTSCH. So was the original policy appropriate, or was it inappropriate?

Mr. KOPPERL. As I think you heard Ms. Vaczy say that this policy was frequently reviewed—I think "frequently" is her word. Frequently reviewed with outside counsel, and it was determined by them that it was adequate.

Mr. DEUTSCH. What about the policy permitting Sam to borrow hundreds of thousands of dollars at a whim from the company? Was that a policy that was an appropriate policy?

Mr. KOPPERL. Sir, those were—we have always had a procedure in place about loans, and we—loans were fully disclosed. The loans were repaid in full, and the loans at least for the past—ever since 1994 or 5 have borne interest at an attractive rate to the company, in fact. So all the money that Sam Waksal may have borrowed was repaid in full, every last penny of it.

Mr. DEUTSCH. So it was an appropriate policy at the time?

Mr. KOPPERL. The policy worked. I felt it was appropriate. I think my colleagues felt it was appropriate.

Mr. DEUTSCH. What about the policy in terms of payments to Sam and Harlan Waksal over $1 million plus stock when the company had not made a penny at that point in time? Was that appropriate reimbursement schedule?

Mr. KOPPERL. Well, those—you're talking about their bonuses?

Mr. DEUTSCH. Well, not just the bonuses but the salaries as well.

Mr. KOPPERL. Salaries and bonuses. Well, the salaries were reviewed by the compensation committee, as were bonuses, and the

achievements that Sam and Harlan had made in growing the company, which became increasingly complex as time went on, these bonuses—salaries and bonuses were reviewed in detail and were considered to be acceptable.

Mr. DEUTSCH. Did you approve the deal to move up the vesting of shares by Sam Waksal?

Mr. KOPPERL. Yes. The board of directors approved it, as did the stockholders.

Mr. DEUTSCH. And that occurred—when that occurred, so they could purchase those stock options and tender them to Bristol? Was that correct? Was that the purpose of it? Right. I mean, the loans of over $100 million.

All right. What were the loans that were available, the loans that were approved at that point, the corporate loans?

Mr. KOPPERL. I'm sorry, Mr. Deutsch. Forgive me. Are we talking about stock options or about loans?

Mr. DEUTSCH. Well, no. Let's talk about the loans.

Mr. KOPPERL. Okay. Thank you. In July, I think it was, of 2001. Isn't that the——

Mr. DEUTSCH. That's correct.

Mr. KOPPERL. The board considered the possibility of making loans to all the directors and decided—determined that this would not—that this would be an appropriate thing to do. We also considered the possibility of extending loans to employees and determined that that would not be—because of the confidentiality of negotiations that were going on at the time, that that would not be an appropriate thing to do.

Mr. DEUTSCH. Besides Harlan and Sam Waksal, was anyone else allowed to borrow money from the company to acquire shares?

Mr. KOPPERL. The directors were, yes, sir.

Mr. DEUTSCH. I'm sorry?

Mr. KOPPERL. The directors were.

Mr. GOLDHAMMER. Board of directors.

Mr. KOPPERL. The board of directors were given that opportunity.

Mr. DEUTSCH. Now, the board supported Sam Waksal in the support with Bristol last winter—and again, I guess I've gotten sort of bits and pieces from the chairman's questioning. At that point you did not know that he had forged loan documents? When Bristol basically had a—wanted to get rid of Sam last winter, were you aware at that point in time that he had forged documents?

Mr. KOPPERL. I believe that the board was advised by our—I'm sorry. Let me start again. I believe that the special committee of the board, which excluded Sam Waksal and Harlan Waksal, that the board was apprised of a possible—I repeat, possible signature forgery issue in early February, and I think that within a few days, they—we took—we took this seriously. We asked our counsel, our outside counsel, to investigate thoroughly and to do so as quickly as would be practicable and report back to the board.

A few days and—I can't tell you exactly, but I would think within a matter of a week or so, the—we received a letter from Peter Dolan, the CEO of Bristol-Myers Squibb, making demands on ImClone and proposing to renegotiate the agreements that—the agreements that existed between Bristol-Myers and ImClone.

Mr. DEUTSCH. Were you aware that Sam Waksal was under investigation by the SEC for insider trading and was also under investigation by this committee at that time?

Mr. KOPPERL. I believe so.

Mr. DEUTSCH. So you—obviously you supported his position in terms of Bristol's request. Why then and not now? I mean, now you've changed that position. What happened? I mean, is he still entitled—you know, he hasn't been proven guilty. Shouldn't—I mean, should he still be leading the company today?

Mr. Goldhammer.

Mr. GOLDHAMMER. The counsel, the counsel sadly was taking a long period of time to come up with this forgery question. At that time, Sam was delivered a Wells Notice and that became——

Mr. DEUTSCH. I'm sorry. He delivered——

Mr. GOLDHAMMER. I believe at that time, right at that time——

Mr. DEUTSCH. The Wells letter?

Mr. GOLDHAMMER. Yes.

Mr. DEUTSCH. Yeah.

Mr. KOPPERL. May I add something to that, Mr. Deutsch?

Mr. DEUTSCH. Yes.

Mr. KOPPERL. The company adopted a thorough process to investigate the allegations against Sam Waksal as they arose. And this was a continuing review in late January, February, March, April and into May. And the Wells Notice that Sam Waksal received from the SEC was the—all along during that time, we decided on balance for the good of the company and particularly the personnel, that we would, if possible, like to retain Sam's services. But the Wells Notice was the final straw and in, I think it was May 22 or 21, we requested Sam's resignation, and he resigned, I think, on May 22.

Ms. DEGETTE. Will the gentleman yield?

Mr. DEUTSCH. My time has expired.

Ms. DEGETTE. I'd ask unanimous consent that the gentleman be given an additional minute so I can follow up on his question.

Mr. GREENWOOD. Without objection.

Ms. DEGETTE. All right. Will the gentleman yield?

Mr. DEUTSCH. I would be happy to.

Ms. DEGETTE. I guess I don't understand, Mr. Kopperl, why it would take all those months for an outside counsel to investigate what would seem to me to be a very simple issue of a forged issuer's letter.

Do you have any insight into that?

Mr. KOPPERL. Well, as I mentioned, ma'am, it was within a few days after the special committee of the board received the information about the alleged forgery that we were hit by the demand—not just a proposal, but a demand by Bristol-Myers Squibb to renegotiate the arrangements between the two companies. And that took approximately 6 weeks to——

Ms. DEGETTE. Okay. But you got a demand from Bristol-Myers Squibb. But in the meantime, you have this forged signature right in front of you.

Why would that take so long to investigate and take action? It seems to me pretty clear-cut.

Mr. DEUTSCH. And if I can reclaim my time for a second. I mean, did you ask Sam Waksal if he forged the signature?

Mr. KOPPERL. We turned it over to our special counsel, sir.

Mr. DEUTSCH. And I assume—did they ask him that question?

Mr. KOPPERL. I don't know what their process was.

Mr. DEUTSCH. I mean, wouldn't that have been an appropriate question to ask?

Mr. KOPPERL. Very possibly.

Mr. DEUTSCH. I mean, very possibly it would be appropriate? You can't say, yes or no? That's the most ridiculous answer I've heard in a very long time here, and we've had everyone. We've had Enron—I mean, we've had WorldCom and that's up there.

I mean, "very possibly." Your CEO, the head of the company, forged a document. This is wacky. I mean, this is wacky. A guy's forging documents and you keep him in charge of the company, and you're outside directors.

I mean, that's the whole issue that we're dealing with here, and the best you can come up with, maybe they might have asked him?

Did you look the guy in the eye and say, "Did you forge it?"

Mr. KOPPERL. I respect your opinion, sir, you know, clearly, but I would like to say that we turned the matter over to a very prominent law firm in New York City and said investigate and come back to us with the results and conclusions of your investigation. And that's what we did.

Mr. DEUTSCH. And how long was that investigation for? How long was the investigation? I mean, what was the timeframe?

Mr. KOPPERL. Well, the investigation, as I recall, had not been completed by the time we asked Sam Waksal to step down, at which point it became moot.

Mr. GREENWOOD. The time of the gentleman has expired.

The gentleman from Florida is recognized for 10 minutes.

Mr. STEARNS. Thank you, Mr. Chairman. And I'd like to turn to part of the insider trading that's concerning the blackout period.

At Tab 19, your policy reads, "There will be periods of time when it is clear that material, nonpublic information is known by several employees, officers and directors of the company. An example would be the making of a seminal discovery in the company's science, or significant results in one of its clinical trials, or the pending announcement of an important strategic alliance for the company."

I'd also like to refer you to December 18, 2001, Tab 20, e-mail from Mr. Gallagher, a member of your legal department in which he writes, quote, "On Tuesday, December 18, 2001, Cathy Vaczy reminded me in a conversation that I'm subject to the insider trader policy of the company. She further informed me that select members of senior management have been aware that the FDA may not accept our BLA, biological licensing application, filing."

Ms. Vaczy, when did ImClone initiate its blackout period prior to the FDA announcement on December 28?

Ms. VACZY. We put a company-wide blackout——

Mr. STEARNS. Can you put that microphone right on.

Ms. VACZY. We put a company-wide blackout in effect on December 21.

Mr. STEARNS. Okay. Is it true that the FDA contacted ImClone on December 12?

Ms. VACZY. I understand there was a conversation on December 12 with Dr. Lily Lee, our Vice President of Regulatory Affairs, and perhaps some other individuals.

Mr. STEARNS. Okay. When they made the contact with him, were you aware what they said to him about Erbitux?

Ms. VACZY. What I learned from this conversation on the 12th, through discussions with other select members of——

Mr. STEARNS. Did you talk to him directly yourself?

Ms. VACZY. It's a woman, Dr. Lily Lee.

Mr. STEARNS. Okay. Did you talk to her?

Ms. VACZY. I don't recall that I spoke to her directly myself.

Mr. STEARNS. But that would be a big deal. If the FDA called her and talked to her about Erbitux, wouldn't that be a big deal?

Ms. VACZY. I don't think so. My understanding is, Lily was in contact with them virtually daily. But I think——

Mr. STEARNS. So you think this was a routine call——

Ms. VACZY. Well, I think many calls were routine. However, this call on the 12th, we did, based on Lily's report to senior management, she stated that this was the first time she had spoken to the FDA where she felt their tone had changed, and she became concerned.

Mr. STEARNS. Well, based upon this call on December 12, when do you think, in your mind, senior management were told about the FDA's decision, impending decision?

When, in your best estimate were they aware?

Ms. VACZY. Oh, well, we—we certainly were not told until December 28 of the FDA's final determination. During the month of December there was really an evolution of certain communications.

Mr. STEARNS. No. But I mean, when were they aware that they might, the FDA might not accept the findings of ImClone? When were they aware of that date?

Ms. VACZY. Well, we formally knew on the 28th.

Mr. STEARNS. No. No. We all know the formal. But what we're trying to do is trying to understand if there's insider trading.

Ms. VACZY. Right.

Well, I would like to say that on the 12th. And I believe that executives from our company have testified to this before in front of this committee that the 12th was important to us, because that was the——

Mr. STEARNS. Tip off?

Ms. VACZY. No.

Mr. STEARNS. No.

Ms. VACZY. It was a time at which the—Dr. Lee reported to management, it's the first time she had any thought that perhaps there was a problem. She referred to it as a "change of tone.".

Mr. WAKSAL. Congressman, if I could help out in this, if possible.

Mr. STEARNS. Okay.

Mr. WAKSAL. I testified at the last hearing, and Dr. Lee was here as well, that around December 12, December 13, we had had a number of conversations internally and with the FDA, and the tone had changed in the discussions we had with them.

In prior conversations, they were continuing to give us guidance as to how we could go ahead and remedy what we considered the documentation issues surrounding the filed BLA. December 12 we no longer got that guidance. They said wait, and we'll get back to you. There was no tipping of any type to us.

But we became concerned, and it was a very small group of individuals who were involved with this. This was not disseminated to management as a whole as the letter in that file indicates. It was a very small, select group of senior executives that were aware of what was taking place with the FDA.

Mr. STEARNS. Would Charles Dunn be one of those senior executives that knew?

Mr. WAKSAL. He would not be.

Mr. STEARNS. Okay. Would Lisa Cammy.

Mr. WAKSAL. Lisa Cammy, she would not be the head of human resources, no.

Mr. STEARNS. Would Tom Gallagher?

Mr. WAKSAL. No. As the memo points out, Tom was not part of that group that knew.

Mr. STEARNS. Would Daniel Hicklin.

Mr. WAKSAL. He would not.

Mr. STEARNS. Okay. And would Nikhil Mehta.

Mr. WAKSAL. He would not.

Mr. STEARNS. Well, it says here he was a member of the regulatory affairs committee.

Mr. WAKSAL. He was involved with the manufacturing component of the submission. Lily Lee was the person who was working and interacted with the FDA; and to my knowledge, he had no information regarding the interaction with the FDA.

Mr. STEARNS. I respect what you're saying, but I'm reading from a list of people who suddenly, on December 14 started unloading a lot of shares, the people I mentioned.

December 14, December 13, December 14, December 14, December 17, December 11, all these people suddenly ImClone officer stocks sales start to be out the door—4,500 shares, 3,500 shares, 5,000 shares, 32,212 shares, 20,000 shares for Thomas Gallagher on December 14, 5,000,—no, excuse me, 5,000 on December 17.

You just—I'm just telling you, looking at this and hearing what Ms. Vaczy says, that not knowing, I would have a hard time—why did all these senior people, these aren't general managers, these aren't drafting managers; these are VP of manufacturing, VP of system facilities, VP of intellectual property, regulatory affairs. I mean, these were senior people, looking at their titles.

And these are not small. They're not selling 100 shares. Some of them are as high as, you know, 32,212. Why would all these senior people suddenly, after December 12, start moving out and selling all this? Is this all coincidental, in your opinion?

Mr. WAKSAL. Yes, it is. And I if could comment for a moment, if you look back over the sales that take place from employees in a company and our company, over the course of the many months, on average, there were around 20, 21 employees, per month that would exercise and/or sell stock.

Mr. STEARNS. In senior management?

Mr. WAKSAL. Across the board, sir. Some in senior management and otherwise. There were certainly many people in senior management as well, but these individuals that you're speaking about—and I just want to go back to the memo from Tom Gallagher; it is very clear in his memo that it was a select group, and I have to emphasize that, a small and select group of individuals.

Mr. STEARNS. So these people that I mention are all a select group?

Mr. WAKSAL. They are a group of individuals who, in fact, were not part of the individuals that had any knowledge regarding the interactions with the FDA, to my knowledge.

Mr. STEARNS. Well, it's just, you know, we have on December 12 contact from the FDA to senior management; and then we have—on December 18 we have some more communication. And then we have on December 21 your e-mail, which is asking for a blackout. And this—let me just read your e-mail.

"As many of you know, the FDA is required to tell us by the end of next week whether the filing of the BLA for Erbitux has been accepted and whether the file will be granted expedited review. Given the importance of this news, we believe employees should not trade ImClone stock until we receive definitized information from the FDA and a press release is issued."

"Accordingly, we have put into effect a company-wide blackout on trading in ImClone stock, as described in Section IV (D) of ImClone's insider trading policy."

So, I see before this blackout a lot of senior people selling thousands of shares of stock, and the FDA contact on December 12; and your argument is that the contact on December 12 was routine and that these individuals, these senior people, were not inside the close group that you considered the higher management, but these were—from their titles, seem to be higher management. And yet they were all selling a large amount of stock prior to the blackout that was instructed on December 21.

And so I'm just finding that a little bit difficult. So I think——

Mr. WAKSAL. If I could just comment, sir?

Mr. FLETCHER. Briefly.

Mr. WAKSAL. I believe that whenever a company's stock goes up as high as ours was going up and it took place several times during the course of that year, on all of those occasions individuals took the opportunity to sell some of their shares or to exercise stock.

And I have to say, we went through an investigation, looked into whether or not there was any sense of insider trading; and the conclusion that we reached, based on the inquiries, was that these trades were not based on inside information. They were not based on nonpublic, material information, and they were done for personal, individual reasons.

And I have to say today that that memo that you point to speaks very clearly about the gentleman, Tom Gallagher, and others not knowing about what was taking place in this BLA process.

Mr. FLETCHER [presiding]. The gentleman's time has expired.

Recognize Ms. DeGette for 10 minutes.

Ms. DEGETTE. Thank you, Mr. Chairman.

Mr. Goldhammer, you've been the chairman of the ImClone board since 1991. Would that be correct?

Mr. GOLDHAMMER. Yes.

Ms. DEGETTE. I think you're going to need a microphone, and now you'll need to turn it on.

Mr. GOLDHAMMER. Hello.

Ms. DEGETTE. That's great.

Mr. GOLDHAMMER. Yes, ma'am.

Ms. DEGETTE. Okay. And in the period that we're talking about here, up until last spring, you and Dr. Sam Waksal and Dr. Harlan Waksal were the three members of the executive committee of the board of ImClone, right?

Mr. GOLDHAMMER. Yes.

Ms. DEGETTE. How long were the three of you the members of the executive committee?

Mr. GOLDHAMMER. Since the company was founded.

Ms. DEGETTE. And that was when?

Mr. GOLDHAMMER. 1984.

Ms. DEGETTE. Okay. So for that whole period of time it was just you three who were the executive committee, right?

Mr. GOLDHAMMER. Yes.

Ms. DEGETTE. And so you were all charged with making all of the decisions between board meetings, as executive committees do, right?

Mr. GOLDHAMMER. Yes.

Ms. DEGETTE. Now, throughout the period—really, throughout the 1990's, Dr. Sam Waksal had a number of loans from the company. I think we already talked about that a little bit, right?

Mr. GOLDHAMMER. Yes.

Ms. DEGETTE. If you'll look at Tab 63 in your binder, it kind of summarizes the loans, and it says on October 1, 1992, there was a promissory note from Sam Waksal for $257,000 plus 10 percent interest; April 1, 1993, $367,000 bearing 10 percent interest—that consolidated the other loan—then on March 22, 1995, $157,000, roughly, bearing 8 percent interest.

And it goes on like that, January 1998, another loan, $130,000; and then December 21, 2000, $282,000, roughly; and then in July 2001, right before the Bristol-Myers deal, Sam Waksal took $18,178,750 in payment for the exercise price associated with the exercise of stock options and warrants, right?

Are you following that? Is this a pretty accurate summary of the loans that Dr. Waksal received from the company?

Mr. GOLDHAMMER. I think so.

Ms. DEGETTE. Now, all throughout this period of the 1990's I think you and also Mr. Landes and others said this company was a small biotech company, but trying to grow, right?

Mr. GOLDHAMMER. Yes.

Ms. DEGETTE. And I assume that capital was always tight in the company, as it always is with small, growing companies, right?

Mr. GOLDHAMMER. Yes.

Ms. DEGETTE. But if you make these loans, even though they're paid back eventually, while the loans are outstanding, that's capital the company doesn't have at that time, isn't it?

Mr. GOLDHAMMER. Yes.

Ms. DEGETTE. Okay. Now, let's talk for a minute about this $18 million loan at the same time Dr. Waksal, Dr. Harlan Waksal, took

a loan for $17 million, the promissory note for $17 million, also for the exercise price for the stock options, correct?

Mr. GOLDHAMMER. Right.

Ms. DEGETTE. And——

Mr. GOLDHAMMER. That's the last one.

Ms. DEGETTE. I'm sorry?

Mr. GOLDHAMMER. I had to go to another page. The answer to that is yes.

Ms. DEGETTE. All right.

Now, there were three people who exercised stock options from that transaction. The two Dr. Waksals and you, right?

Mr. GOLDHAMMER. Right.

Ms. DEGETTE. And there were only three people that exercised stock options, right?

Mr. GOLDHAMMER. I think there were four.

Ms. DEGETTE. Four? Who was the fourth?

Mr. GOLDHAMMER. Oh, exercised options.

Mr. WAKSAL. There were many people who were exercising options.

Ms. DEGETTE. I'm sorry. Who borrowed money?

Mr. WAKSAL. There was a fourth person who borrowed money, as well, I believe.

Ms. DEGETTE. And who was that?

Mr. WAKSAL. Dr. Arnie Levine.

Ms. DEGETTE. Okay. But three of the four people who borrowed money to exercise the options were the three members of the executive committee of the board of directors, weren't they, Mr. Goldhammer?

Mr. GOLDHAMMER. Yes, they were.

Ms. DEGETTE. Okay. Now, there was a great concern about some of Dr. Sam Waksal's spending habits throughout the period of—well, throughout the 1990's. Would that be fair to say?

Mr. GOLDHAMMER. I would say that's fair.

Ms. DEGETTE. And why would you say that Mr. Goldhammer?

Mr. GOLDHAMMER. Well, because in the beginning, as you say, it's a small company——

Ms. DEGETTE. Uh-huh.

Mr. GOLDHAMMER. [continuing] started off with about 20 people. Even through the middle of the 1980's, late 1980's, we only had 50 or 60 people; so it was a small company.

Ms. DEGETTE. Right. And you're worried about people—the board is worried about people—about keeping costs under control, right?

Mr. GOLDHAMMER. Yes.

Ms. DEGETTE. If you could take a look—and, Mr. Kopperl, it'll probably be good for you to take a look—at Tab Number 5, which is the minutes of the audit committee meeting held on February 12, 1998, which was several years ago. Take a look at that second page.

I was particularly interested in Number 6 because, over the years, I've dealt with a lot of corporations; and I've got to be honest, I've never seen a document like this where the audit committee of the board of directors has got to tell the CEO that, for example, they can only charge $50 to $100 of wine per bottle, or that they can't buy sporting tickets except exceptional circumstances, or that

under "Lodging"—clearly Motel 6 is neither necessary or appropriate; however, five-star European hotels, such as the Crillon, and occupying a suite are inappropriate unless a significant discount can be obtained.

Have you ever seen a corporate travel policy that goes into these specifics, Mr. Kopperl?

Mr. KOPPERL. I have not.

Ms. DEGETTE. And what was the purpose of enacting such a policy?

Mr. KOPPERL. I'm glad you asked that.

Ms. DEGETTE. I am too.

Mr. KOPPERL. We, ever since I joined the board, have had an expense account procedure. The—beginning in 1994, this procedure was codified in a lengthy—I'll call it "booklet," a document that explained what the procedures were for expenses to be reimbursed. And this "booklet," if you will, is still valid today.

Ms. DEGETTE. And when was the booklet promulgated?

Mr. KOPPERL. In 1994.

Ms. DEGETTE. Okay.

Mr. KOPPERL. Okay?

Ms. DEGETTE. But this document——

Mr. KOPPERL. I'll come right to that if you just give me one more moment.

Ms. DEGETTE. Yeah.

Mr. KOPPERL. Beginning in probably 1996 or -7, I was asked by the board or by the other—I was, anyway, by the other members of the audit committee to review Dr. Waksal's, Sam Waksal's expense account.

In 1996, we instituted a very important change, and that was that all charges that Sam Waksal ran up on his American Express credit card, which I think was the only credit card, corporate credit card had to be paid by Sam Waksal personally. So if he wanted anything, if he wanted the company to pay anything, he had to come to the company and ask for reimbursement.

Ms. DEGETTE. Right.

Mr. KOPPERL. It was not that the company was paying the bill and then going to Sam Waksal and asking for reimbursement.

Ms. DEGETTE. You need to summarize fast, because I don't have a lot of time.

Mr. KOPPERL. So there were a lot of expenses for which he asked us to reimburse him, and we—and we went through our financial department, which lumped expenses into three different categories: clearly business expenditures, clearly personal expenditures and those that needed to be discussed.

I was the guy who was supposed to review those, all of those, and I decided in late January 1998 that this was taking far too much of my time and that we had to come up with a better—a better system, and that's why you have this.

Ms. DEGETTE. Okay, great. Thanks.

But see, here's the thing: The 1992 loan for $275,000 was for personal expenses run up on the credit card. Then you have the 1994 policy, then you have this audit committee meeting in 1998. It's like you guys kept doing stuff, but it never changed.

And I just have one final kind of comment, and you can respond, any of you, Mr. Goldhammer, if you want. Here you have a forgery which Mr. Landes, a lawyer, says, well, it's because he didn't understand a procedure. I never knew a standard procedure to be a forgery.

In 1991, then you have a whole systematic taking out of money and loans, abuse of credit card charges on the corporate credit card for almost a 10-year period. Then you have another forgery. Then you have insider trading around Christmas of last year, which I haven't even gotten to ask about. And it still takes the board almost 6 months to fire the guy, and he's only fired 2 weeks before criminal charges are brought.

I am—I'm just—I'm stunned, and I'll yield back the balance of my time.

Mr. GREENWOOD. The Chair thanks the gentlelady and recognizes the gentleman from Kentucky for 10 minutes to inquire. And before doing so, I would note that I believe there will be two votes here, so at the end of Mr. Fletcher's questioning, we'll probably recess until 3:30.

Mr. FLETCHER. Thank you, Mr. Chairman.

My concern—I wasn't here for all of the testimony. I've certainly read through and reviewed some of it. I wanted to address the concerns I've got about looking—during this period of time particularly when the studies were going on, there seemed to be a lot of promotion going on about the effectiveness of Erbitux and what it was going to do in the treatment of colon cancer particularly.

At the same time, we have this scientific advisory board and a lot of publicity goes out of certainly the distinguished members of that board. And let me ask, I know—Dr. Mendelsohn, I believe, is a member of that board. Is that correct?

Mr. MENDELSOHN. Yes, that's correct.

Mr. FLETCHER. And certainly you have a very distinguished record as being, I guess in your testimony, President of and Professor at the M.D. Anderson Cancer Center at the University of Texas, so you probably have a lot of experience, if not personally, at least from a management standpoint, of overseeing cancer trials, protocols, I assume.

Are those done at M.D. Anderson cancer center?

Mr. MENDELSOHN. Yes, they are.

Mr. FLETCHER. Let me ask you, as a member of that scientific advisory board from 1997 to 2001—is that right?

Mr. MENDELSOHN. And earlier, yes.

Mr. FLETCHER. Okay. Who were some of the other members on that board?

Mr. MENDELSOHN. Dr. Zvi Fuchs, Dr. Tom Deuel, Dr. Tom Shenk, Dr. Arnold Levine and myself, and for a while, Dr. Fred Sparling and Dr. Gerald Keusch, K-e-u-s-c-h.

Mr. FLETCHER. It would seem to be a very distinguished group and people well known in the oncology and immunology communities; is that a fair assessment?

Mr. MENDELSOHN. Yes.

Mr. FLETCHER. Let me ask you why the advisory board was established.

Mr. MENDELSOHN. The scientific advisory board, when I joined it in 1992, had the main function of reviewing the research that was going on at ImClone because they were doing research, studying not only Erbitux.

Well, they weren't even studying Erbitux; they didn't have it. They were studying a variety of approaches to treating cancer, and they were also looking at licensing opportunities to bring in compounds. And we would review the research that others were doing that the company might license, and we would review the company's laboratory research program.

Mr. FLETCHER. Let me ask you during the period—I mentioned 1997 to 2000, did that—the scientific advisory board meet during that period of time?

Mr. MENDELSOHN. Up until around 1996 or 1997, it met as a group regularly. After 1997, the company's emphasis shifted more toward two or three products that they were actually bringing into clinical trials, and the scientific advisory board was consulted with individually or in groups of two or three, as needed.

Mr. FLETCHER. So—it did not meet as a group of six or seven?

Mr. MENDELSOHN. No. It did not.

Mr. FLETCHER. Let me ask you, because during—you know, the problems I see here and as we had the previous hearing on this was that we've got some very distinguished and able members on the board, on the scientific advisory board as well, and yet all the time we had a flawed protocol. We had protocol that wasn't being followed even in the trials at some very distinguished centers.

Were any of those trials being done at M.D. Anderson?

Mr. MENDELSOHN. The registration trials on colon cancer were not being done at M.D. Anderson, but other trials were done at M.D. Anderson.

Mr. FLETCHER. Let me ask you, it seems rather odd to me that you've got a scientific advisory board that is really made up of some very distinguished members and yet, and I assume their responsibility, somewhat, was to oversee the scientific side of these protocols that were going on. And yet they were so flawed and yet the whole time when the scientific advisory board was not meeting, not overseeing the protocols—or at least if they were, they were doing an ineffective job—you have the company and the board still promoting this product as being very promising in the future.

Mr. MENDELSOHN. You've asked a number of questions.

First of all, the scientific advisory board members that I named were nearly all Ph.D.s and were much more focused on the preclinical work than the clinical work.

The protocol was not reviewed by that board for flaws at all. It was not the business of that scientific advisory board to review the protocol.

Mr. WAKSAL. Congressman, if I could interrupt for a moment——

Mr. FLETCHER. Yes?

Mr. WAKSAL. A couple of points.

First, the statement made that the protocol was obviously flawed: The company, the investigators who were working on that protocol did not feel, and I don't believe—feel today that that protocol was flawed.

Second, the promotional aspects of using our SAB for promotional reasons that had not been done by the company: I think it's—it is not a fair characterization to state that the company was out promoting a flawed protocol or a flawed effort. What we were doing was, we were working to move this drug forward through clinical studies, and I believe we were doing so in an appropriate way.

Mr. FLETCHER. Let me interrupt you just a minute, Dr. Waksal, because I——

Mr. WAKSAL. Please.

Mr. FLETCHER. I want to make sure—you're saying that you felt like ImClone during this period of the trials of Erbitux was practicing sound science during the process of getting FDA approval, or at least to the extent that you were working on the phase II studies.

Mr. WAKSAL. Well, let me emphasize that. I strongly believe we were doing sound science and appropriate science the entire time we were working and moving this process forward. Absolutely.

Mr. FLETCHER. Well, let me say, when we spoke to the parent company, and the way they oversee protocols, and when we—you were here in the previous hearing; we talked. There was apparently very little oversight. There was a great deal of information put out on how promising this drug was.

Mr. WAKSAL. I'm sorry, sir. What information was put out that was inappropriate on how promising the drug was?

Mr. FLETCHER. Well, I think, given the fact that the emphasis seemed to be more on the marketing of Erbitux than it was on overseeing the trials——

Mr. WAKSAL. I don't believe that's the case. I believe we were working very hard.

We're a very small company, very small company that used clinical research organizations, individuals with great knowledge in this area, to oversee these studies and protocols; and we worked closely with them to move it forward.

Mr. FLETCHER. I think clearly from what the FDA presented and how the protocols were not followed, and from the last hearing we had where the oversight, I think, maybe it's due—because of a small company or whatever, but it certainly came far short of what was necessary to ensure it.

And yet we have—even here, someone has suggested that, you know, the board maybe should—the scientific advisory board should meet.

Let me read this:

"Dear Sam and Harlan:

"I'm sorry there's been some turbulence and possible misunderstandings relating to the final approval of C225, Erbitux. I know this must be distressing for everybody since many outsiders apparently are suffering from a lapse in confidence in the company as a result of various public statements and disclosures. I suggest that your scientific advisory board could help if you were to bring us together to review the situation in some detail.

"I realize that I am not a cancer investigator, but I think the board could be very useful at this particular time and I suggest that you do bring us together again for this purpose."

Do you recall this letter?

Mr. WAKSAL. Yes it's from Dr. Fred Sparling. It was very kind of him to reach out to us.

Mr. FLETCHER. That's correct. And yet, was his advice followed?

Mr. WAKSAL. Well, his advice was that we pull together the scientific advisory board.

We have much greater depth with a great deal of other clinical advisors, that have expertise in this area, that we worked with to start to address the issues and concerns.

Now clearly, sir, one of the problems we had with our clinical study was that we had faulty documentation. That is something that I talked about at the last hearing, something that I regret took place and something we are still working to make sure is in place and corrected.

Regarding the advice we were receiving, we had great expertise from the oncology community, from individuals with great expertise, from all of these centers, 25-plus centers, who were working with us to make sure that our protocols were well defined and moving forward appropriately.

Mr. FLETCHER. Let me just say that we have some letters from Dr. Sparling saying that basically he ended up resigning, I believe because of the lack of response that he received; or at least, I think he felt like the scientific advisory board was not being taken seriously in the role, and he eventually resigned.

Let me ask Dr. Mendelsohn something. I mean, there's a tremendous expertise on this board, and I grant that. And, to me, it's amazing that with this expertise, you've got such a promising drug—which still seems promising to me, from the literature—and yet, at the same time, you seem to have a company that has more emphasized the marketing and being concerned about that than making sure that the science was done well.

You have mentioned that there was problems with the data collection. There were patients that were taking it in the protocol that did not meet the design of the protocols or the standards of the protocol. Those are the very basic elements of research. And folks like yourself that have been in this business a long time know that throws out all of the research and makes it really lack credibility.

Mr. MENDELSOHN. The protocol was developed with the advice of medical oncologists from some of the world's greatest institutions, 27 of which participated in carrying it out. There were numerous meetings. I went to those meetings to give background. I often attended meetings to give background and the scientific rationale for what we were doing; and then these various experts from many institutions around the country, that you're aware of because you've seen the list, would get together and work with the company.

Then the company also brought in expert consultation from individuals who worked closely with it and developed a protocol. The protocol was managed through a——

Mr. FLETCHER. When did you first find that the protocol wasn't being followed as it was laid out, and when some of the data collection was inadequate?

Mr. GREENWOOD. If the gentleman would yield for a moment. We have under 3 minutes to make this vote, two votes with regards to Iraq, so it's important that we get there.

So I'm going to ask that we recess at this moment, and we'll return at 3.

[Brief recess.]

Mr. GREENWOOD. The subcommittee will come to order.

Mr. Stupak.

Mr. STUPAK. Thank you, Mr. Chairman.

Dr. Waksal, the questions that Mr. Fletcher asked and one that bothers a lot of us up here, we continue to hear you say, look, there is no problem with Erbitux, it is just some missed documents, missing documents, things like that. But yet it continues to be—in January 2002, the Cancer Letter to Trade Journals said—put down some of the reasons why the FDA did not approve your fast track authority there. And those are some very serious problems with the protocol and with your application. It is not just missing documents.

And in fact, it really raised some very, very serious questions. And that is what all of us believe up here. You continue with this line that, well, it is just this or this missing. What do you base that on?

Mr. WAKSAL. Well, first of all, let me say that I am not saying that there were not problems with the biologic license application. The question is, I keep saying there are no problems with Erbitux. Well, indeed there were problems with the application.

Mr. STUPAK. There is serious problems with your protocol.

Mr. WAKSAL. Well, no, sir. There were problems with the excuse of a protocol. There were problems with the documentation.

Mr. STUPAK. High rates of patient ineligibility. There were so many waivers given. Even Bristol-Myers Squibb, who was your partner in this whole thing, their independent radiology review showed that strict scrutiny of the study data yield only a response of 12.5 percent, but yet you are promising 22 percent.

Mr. WAKSAL. Well, that is not true, sir. I never promised 22 percent. What we reported—what we reported was very clear. The scientists that were involved in the trial, the oncologists reported at their sites based upon——

Mr. STUPAK. Based upon studies which showed high rates of patient ineligibility and waivers given to patients. So the study that you relied upon with 22 percent wasn't—and you couldn't achieve it with all these waivers and high patient ineligibility.

Mr. WAKSAL. Well, if I could comment. Again, with respect to response rate, the response rate at the independent sites and then subsequently done by an Independent Radiology Advisory Committee showed the response rate in the 19 to 20 percent range. Now, whenever you get that information, the next question is, were are all those patients eligible? Were all those appropriate? There were deviations. In every study, in every protocol there are deviations. We just——

Mr. STUPAK. Not at the rates we have seen here.

Mr. WAKSAL. Well, while one could argue whether the rates here were higher than others, I have to state that every protocol, every study has protocol violations and deviations. Most importantly, the comment that only 12.5 percent response rate is, in my opinion, understating the real value of what was shown. It was in a worst-case scenario.

Mr. STUPAK. This is Bristol-Myers Squibb's study that says it is 12.5 percent.

Mr. WAKSAL. Yes, 12.5 percent.

Mr. STUPAK. That is your partner in this whole thing who would want to see it to be a very successful drug and would not downplay the number.

Mr. WAKSAL. They didn't downplay the number. As you remember, when they sat here, they said they didn't look at 12.5 percent as a failure. They believed 12.5 percent was a very excellent response rate in this type of drug in this kind of patient population.

Mr. STUPAK. Well, not really. That is not what they said, because Erbitux was being used with other combination drugs, and you couldn't make a determination whether it was the Erbitux which was fighting the cancer or the combination of the other treatment.

Mr. WAKSAL. Well, that is the real question that we are trying to identify right now. As you know, we did a single agent study. And with the single-agent study, we had a 10.5 percent response rate. And that work is continuing to go forward.

Mr. STUPAK. If it is just missing data and improper documentation and not unusual numbers, in your estimation, have you ever rehabilitated this application to get it renewed again by the FDA?

Mr. WAKSAL. Well, the world has changed.

Mr. STUPAK. Well, no. Yes or no. That is all.

Mr. WAKSAL. Well, the answer is, yes, we are doing so. We are rehabilitating the study.

Mr. STUPAK. You haven't done it. So if it is just simple missing documentation, why is it taking so long?

Mr. WAKSAL. Well, we have collected the documentation. And what we are doing right now, before going forward irresponsibly, to review anything without the guidance of the FDA, we have been in continued meetings with the FDA to get their appropriate guidance as to the right way to reevaluate the data and the documentation in this trial.

Mr. STUPAK. Who is your—who is ImClone's P R person that they get you all this free advertisement on 60 Minutes and USA Today?

Mr. WAKSAL. Well, if I could just comment. The 60 Minute story was a very strong and negative story about ImClone. It was about compassionate use. And we did not participate in any way. And the other one that was mentioned was a Business Week article.

Mr. STUPAK. Sure. But my question is——

Mr. WAKSAL. I have to say, the author is here today. And the company had no role at all in moving that forward.

Mr. STUPAK. I don't want you to stall on my time. My question was, who was your P R firm?

Mr. WAKSAL. We do our own invested relations and PR internally.

Mr. STUPAK. So ImClone got the USA Today articles, the Business News articles, the 60 Minutes article?

Mr. WAKSAL. Well, actually, it is the journalists that initiate those articles. We went ahead and cooperate with their journalism. We cooperate with newspapers, journalists, et cetera, while the stories are being done.

Mr. STUPAK. So the promotions we have seen are basically international ImClone putting forth their spin on their Erbitux.

Mr. WAKSAL. Well, actually, I just said that that is not. The case the company hasn't put forward a spin at all on Erbitux. We have relied on data from reputable centers, from reputable studies to disclose what is taking place with this drug and how it is being used in patients.

Mr. STUPAK. Were you at the meeting when you sat down with the FDA before they granted you the fast track authority? Did you go to that meeting?

Mr. WAKSAL. The meeting in August 2000?

Mr. STUPAK. Right.

Mr. WAKSAL. Yes, I was.

Mr. STUPAK. And who was with you from ImClone?

Mr. WAKSAL. We had a large group of people there. We had Dr. Mike Needle. There was a long list. And I don't have those names right in front of me, but I would be happy to provide them to you.

Mr. STUPAK. If you would, that would be great.

Dr. Mendelsohn, how much time have you spent working on Erbitux?

Mr. MENDELSOHN. I have been studying Erbitux—I produced Erbitux in my laboratory in the early 1980's. And until the year about 1998, I was studying it in a laboratory that I ran or collaborated with.

Mr. STUPAK. Can you tell us when Erbitux first sought to find someone to manufacture it, to get it licensed and approved through the FDA?

Mr. MENDELSOHN. The first contact was in the middle to late 1980's.

Mr. STUPAK. And so it has been well over 10 years in trying to get this drug manufactured?

Mr. MENDELSOHN. That is correct.

Mr. STUPAK. And why the difficulties in getting it?

Mr. MENDELSOHN. In the 1980's, the company that licensed Erbitux, which was C225, from the University of California was——

Mr. STUPAK. Was that Ely Lilly?

Mr. MENDELSOHN. That was originally Hybritech, which was bought out by Ely Lilly.

Mr. STUPAK. Okay.

Mr. MENDELSOHN. Just flashback to that period, no one believed that monoclonal antibodies were going to be that important. And the concept of blocking a growth factor receptor, which was our idea, was still very novel. Hybritech was bought by Ely Lilly. They had had a bad experience with another antibody, and decided not to pursue things further. And actually, the University did due diligence and got the license back from Ely Lilly. And at that point, ImClone took the license from the University of California with a more aggressive posture.

Mr. STUPAK. And you still have confidence in this drug?

Mr. MENDELSOHN. Yes, sir.

Mr. STUPAK. Can the application be rehabilitated, or is it going to take more time to get it in a position where it can be presented to the FDA?

Mr. MENDELSOHN. In my opinion, the application is ready to be rehabilitated. But I believe——

Mr. STUPAK. Did you work with Bristol-Myers Squibb this time, or did ImClone do it on its own again?

Mr. MENDELSOHN. Bristol-Myers Squibb and ImClone have collaborated closely on this. And I am very pleased about that.

Mr. STUPAK. All right.

Ms. Vaczy.

Ms. VACZY. Yes.

Mr. STUPAK. I am looking at—Mr. Stearns had asked you some questions along these lines about your memo you did back, under Tab 21, on the companywide blackout for no trading for a week because you were expecting to hear something back from the BLA on Erbitux. Have you ever done one of these before for ImClone?

Ms. VACZY. A companywide blockout?

Mr. STUPAK. Tab 21.

Ms. VACZY. We have done blackouts before. Yes.

Mr. STUPAK. For ImClone?

Ms. VACZY. Yes.

Mr. STUPAK. Why did you do this one on December 21, 2001 at 3:30 in the afternoon, which happens to be a Friday? Why would you do it?

Ms. VACZY. Well.

Mr. STUPAK. The week is over. The market is ready to close, close in about 22—34 minutes.

Ms. VACZY. December was a very busy time, and there was a lot going on. And the situation with the BLA was——

Mr. STUPAK. Can you turn on your mike or either pull it up a bit? I can hardly hear you.

Ms. VACZY. The situation with the BLA was evolving. And it was not until December 20 that we had a certain communication from the FDA that got us sufficiently concerned that we felt it was appropriate that no one within the company trade any longer.

Mr. STUPAK. Well, then were you aware that the stock trades that went on prior, between December 12 and 20 then that Mr. Stearns pointed out to you the list of?

Ms. VACZY. I am aware of them now. I would need to look at the list to say what I was aware of.

Mr. STUPAK. So you didn't know anything about it back then?

Ms. VACZY. I would need to see the list to know specifically what I knew at the time.

Mr. STUPAK. Well, it is Tab number 1 in your book there. It is on the second page. It gives some dates of all these sales. The third page has quite a few of them.

The point being, as Mr. Stearns pointed out in his questioning, that there was a lot of people who moved a lot of stock between December 12 and December 21.

Ms. VACZY. Well, I think what—as Dr. Waksal had mentioned, we had previously submitted to the staff of the committee. It was by no means an unusual number of employees engaging in option exercises in sales in December than prior months. So we didn't consider it unusual activity. And the individuals, as we were discussing with the Tom Gallagher e-mail and his reference to only

a select group of senior management having any information, none of those people are on this list.

Mr. STUPAK. Well, tell me, when did you issue another one of these blackout orders, companywide blackout orders for ImClone? Give me another time.

Ms. VACZY. Name a previous time?

Mr. STUPAK. Yeah.

Ms. VACZY. Well, I think just—could I give you sort of an explanation of how we have typically administered——

Mr. STUPAK. No. I just want to know another time when you have done it.

Ms. VACZY. Okay.

Mr. STUPAK. So I can go back and make comparisons between those who sold in and those who sold out.

Ms. VACZY. Okay. I know that one was issued companywide when the company entered into a license agreement with Mark Cage, E A A.

Mr. STUPAK. And when was that?

Ms. VACZY. That was—I believe it was December 1997.

Mr. GREENWOOD. The time of the gentleman has expired.

Mr. STUPAK. Thank you, Mr. Chairman.

Mr. GREENWOOD. The Chair recognizes himself for 10 minutes. And let me return to the board members, if I might.

On March 26 of this year, the press reported that Sam Waksal had failed to report 50 stock transactions over a 10-year period. The question is, did you see this article? And, were you aware of these allegations before the article was published? Any of the members of the board?

Mr. GOLDHAMMER. Well, I saw the article. I was unaware that he never filed a Form 3.

Mr. GREENWOOD. Anything different from Mr. Kopperl or Dr. Mendelsohn?

Mr. KOPPERL. I also saw the article and was not aware. However, I would point out that the company had always had a procedure in place. All employees, officers, and directors were very aware that. And it worked.

Mr. GREENWOOD. Except in these instances, to your knowledge? Dr. Mendelsohn.

Mr. MENDELSOHN. I don't remember when I was made aware of it, but it was around that time. But I don't remember whether it was through the company meetings or through the media.

Mr. GREENWOOD. But you weren't aware of it at the time?

Mr. MENDELSOHN. Right.

Mr. GREENWOOD. On March 20 of this year, Sam Waksal appeared before the Securities and Exchange Commission to give sworn deposition testimony, and invoked his fifth amendment privilege against self-incrimination. On the next day, March 21, ImClone's independent directors recognized that Sam Waksal had a personal constitutional right to refuse to answer the SEC's questions, but decided it was not appropriate for the board to leave Sam Waksal in place as president and CEO in circumstances where he had refused to answer questions put to him by the SEC.

The next day, on March 22, Sam Waksal reversed his decision on asserting his privilege, and wished to testify before the SEC. Is that your understanding of those facts, as I have set forth, correct?

Mr. MENDELSOHN. Yes.

Mr. GREENWOOD. And as a result, Sam Waksal remained CEO of ImClone; is that correct?

Mr. MENDELSOHN. Yes.

Mr. GREENWOOD. One of ImClone's directors, Richard Barth, dissented from the board's actions and resigned from the board on April 2, 2002, because he thought Sam Waksal should be replaced as CEO; is that correct?

Mr. GOLDHAMMER. Yes.

Mr. MENDELSOHN. I don't know why he resigned. But he certainly was——

Mr. GREENWOOD. Okay.

Mr. MENDELSOHN. [continuing] making that statement.

Mr. GREENWOOD. Perhaps you can turn to Tab 40 in your binder. That is just his letter of resignation. It doesn't go to his motive.

Sam Waksal's personal financial problems resulted in ImClone issuing several promissory notes to extend loans to Dr. Waksal because of his use of corporate credit card for personal expenses. We have gone over some of that. That is correct. Is that right?

Mr. MENDELSOHN. Yes.

Mr. GREENWOOD. Due to Sam Waksal's history of irresponsibility and using his corporate credit card, ImClone imposed special procedures to review Sam Waksal's expenses and determine what should be reimbursed. We have already discussed that as well.

Mr. MENDELSOHN. Yes.

Mr. GREENWOOD. You agree with that? Given all of these problems that you knew about in April 2002, you still retained Sam Waksal as CEO, and you gave him a bonus of $415,000, which, had he been terminated as advocated by Richard Barth, ImClone would not have been obligated to pay; is that correct?

Mr. GOLDHAMMER. That was a payment for 2001. It was paid in 2002, as this began to unravel.

Mr. GREENWOOD. But what——

Mr. KOPPERL. Mr. Chairman, if I may. We had a contractual obligation to pay Sam Waksal a bonus. I think the sum actually was $450,000. But whatever it was. Prior to entering into the Bristol-Myers Squibb transaction, Bristol insisted that employment contracts be negotiated and put in place with Sam Waksal, Harlan Waksal, and two or three others. And it was under that, the terms of that agreement with Sam Waksal that the company was obligated to pay.

Mr. GREENWOOD. And you feel that that obligation existed despite his conduct? You didn't feel that he had breached his end of the bargain?

Mr. KOPPERL. As of that time, our attorneys advised us that we should make the payment.

Mr. GREENWOOD. All right. The April 15, 2002 issue of Fortune reported that an investigative report showed that Sam Waksal—quote: "Sam Waksal seems to have developed a pattern of forming partnerships for real estate, restaurant, and small business ven-

tures, and then borrowing money from these ventures and not paying it back."

Over the past 20 years, the report shows dozens of lawsuits and tax liens have been filed against Waksal by the IRS, New York State, American Express, banks, and brokers, arts galleries, contractors, and individuals. And if you want evidence of that, you can look at Tab 41. Did you see the article in April? And, were you aware of these allegations before the article was published?

Mr. KOPPERL. I had better look, because I don't know.

Mr. GOLDHAMMER. Before the—I mean, before this article was published?

Mr. GREENWOOD. Right. Were you aware of any of this litany of problems that the CEO of your company had for 20 years, where he had dozens of lawsuits against him, tax liens filed by the IRS, New York State, American Express, banks and brokers, art galleries, contractors, and individuals. My question is, were you aware that he had this long history of financial irregularity?

Mr. GOLDHAMMER. Yes. I was aware that he had a lot of problems with his personal finances. I didn't know about every specific.

Mr. GREENWOOD. Let me ask you this, Mr. Goldhammer. I have constituents in my district, and we all do, who lost money on ImClone, who bought ImClone stock because they believed it was a promising company. They lost a lot of money. Now, your job obviously as a member of the board of directors, as chairman of the board, was to protect them, to protect the value of their investment. And I am wondering how—given what you have just said, that you were aware that he had this long tortuous history of financial mismanagement, how did you see that keeping him on in his position as CEO of this company was consistent with your duty to protect the investors in the company?

Mr. GOLDHAMMER. Well, first of all, we talk about these loans that we gave him. We did not give him loans.

Mr. GREENWOOD. That is not what I am talking about in this.

Mr. GOLDHAMMER. Okay. Waksal, in the last—Sam Waksal, in the last, I would say 2 years or so, the last couple years——

Mr. GREENWOOD. Turn your microphone toward you.

Mr. GOLDHAMMER. In the last 1½, 2 years, that he seemed to be out of his financial problems. He wasn't coming to me to try to get loans to help him, you know, et cetera, et cetera. And I think it is because he was borrowing a lot of money from banks. I am guessing that. I don't know that. But I know his—he had a lot of securities, and I know he would probably have no hesitation in borrowing money against it.

Mr. GREENWOOD. But did you have moments as a member of this board where you thought to yourself, is this guy worthy of our trust as the CEO of this company, given his lifestyle? What—did you have times where you worried about whether or not this company and its future and the fate of its—the patients waiting for its product, that he was the right guy for this job?

Mr. GOLDHAMMER. Yes, I have.

Mr. GREENWOOD. And did you share that? Was that an opinion, as far as you know, that was held by other members of the board of directors?

Mr. GOLDHAMMER. I just can't answer that.

Mr. GREENWOOD. Have you ever had discussions with any other board members where you guys would have a drink and say, I don't know about this guy. He is—really seems to be——

Mr. GOLDHAMMER. Not really.

Mr. GREENWOOD. No? Mr. Kopperl, Dr. Mendelsohn, either one of you have such concerns?

Mr. KOPPERL. The board actively considered whether to continue Dr. Sam Waksal as the CEO, beginning——

Mr. GREENWOOD. When was that?

Mr. KOPPERL. Beginning in January.

Mr. GREENWOOD. Well, that was after all of this, after the insider trading issue and so forth. But I am talking about in all of the—the litany goes on and on about financial irregularities with Sam Waksal. And my question to you as a board member is, as you observed this behavior, this conduct, did you have moments as Dr.—as Mr. Goldhammer did, when you wondered whether he was—his judgment was sound enough to run this company and protect its investors?

Mr. KOPPERL. We—I speak for myself—regarded Sam Waksal as the visionary who started the company, and in particular, enabled Erbitux or C225 to be brought to ImClone and to develop that.

Mr. GREENWOOD. So he was the company.

Mr. KOPPERL. So he wasn't—if you mean was he the whole company? No, he wasn't. But——

Mr. GREENWOOD. Not literally.

Mr. KOPPERL. Of course. But I mean, we figured—we felt that he——

Mr. GREENWOOD. Was he indispensable?

Mr. KOPPERL. That he was largely indispensable. And that also, because there were additional drugs in the pipeline.

Mr. GREENWOOD. Let me ask a final question. On September 27 of this year, an article from the Wall Street Journal entitled "Four Prestigious Labs Ousted Waksal for Questionable Work" outlines a number of allegations about improper research practices by Sam Waksal at Stanford, the National Cancer Institute, Tufts, and Mt. Sinai. And that article is in Tab 58 if you want to look at it. The question to the board: Were you aware of any of these allegations before the article was published?

Mr. KOPPERL. I was not, for one.

Mr. GOLDHAMMER. I was not.

Mr. GREENWOOD. Mr. Goldhammer says no. Dr. Mendelsohn?

Mr. MENDELSOHN. A similar story appeared in Vanity Fair during the summer, which I read. So that was when I was first made aware of it.

Mr. GREENWOOD. Did that cause you concern?

Mr. MENDELSOHN. Certainly.

Mr. GREENWOOD. Did you act upon those concerns?

Mr. MENDELSOHN. He was no longer running the company.

Mr. GREENWOOD. Okay. So it was——

Mr. MENDELSOHN. This past summer.

Mr. GREENWOOD. It was this past summer?

Mr. MENDELSOHN. Right.

Mr. GREENWOOD. That was the first you learned of any of this?

Mr. MENDELSOHN. That is correct.

Mr. GREENWOOD. My time has expired. The Chair recognizes the gentleman from Florida.

Mr. DEUTSCH. Thank you, Mr. Chairman.

Dr. Mendelsohn, if I can actually follow up on what the chairman was just saying. You licensed Erbitux, ImClone, in 1993 after joining their scientific advisory board in 1992. The article that the chairman referred to states again there are at least four institutions that Sam Waksal was asked to leave, Stanford, National Cancer Institute, Tufts, Mt. Sinai, in each case because of suspicion of dishonesty in his research.

When you licensed your product or your invention or your research, did you do any kind of due diligence about Sam Waksal before agreeing to place the intensity, the—your idea in his hand?

Mr. MENDELSOHN. Congressman, let me explain that the patent for the invention was held by the University of California. I had absolutely nothing to do with the negotiation of the licensing. Dr. Waksal asked me who had the patent, and I told him. And I told him, you will have to contact the Patent Office at the University of California to negotiate. And the entire negotiation was done without my participation.

Mr. DEUTSCH. So you are not aware of any kind of due diligence that they would have done?

Mr. MENDELSOHN. I am unaware of what they did. That is correct.

Mr. DEUTSCH. I mean, would it have been appropriate for them to have done some type of due diligence?

Mr. MENDELSOHN. They may well have. I just don't know. I mean, I was no longer at the University of California at that time, and they controlled the patent.

Mr. DEUTSCH. I mean, it sounds like this is, to some extent, your life's work. I mean, you have obviously a great deal of pride and personal time, and besides finances, invested in this.

Mr. MENDELSOHN. That is correct.

Mr. DEUTSCH. And obviously, I think you are sincere in trying to get the product into use in America and throughout the world. Obviously, the company that—if it was licensed, it would be a key ingredient in that. I mean, were you concerned about what type of company you were licensing the product?

Mr. MENDELSOHN. Yes. I was certainly concerned. And, of course, the license had been held by a major pharmaceutical company that did not move the antibody forward. I had talked with a number of other pharmaceutical companies who were not interested in moving this idea forward. And, frankly, I was delighted when I met Dr. Sam Waksal that he quickly saw that this wasn't just immunotherapy with an antibody,but that we were attacking an oncogene product called the EGF receptor, which is relevant in large numbers of human cancers and might be an attractive thing to bring forward.

So when he contacted the University of California, and I knew he was doing that, I was delighted that there was somebody who seemed to have the energy and the vision to try to bring this forward. It was a small startup company instead of a big drug company, but I had found no one else to do it.

Mr. DEUTSCH. Dr. Mendelsohn, in the tendered offer by Bristol-Myers last year, you made $6.3 million off the sale of 20 percent of your ImClone holding to Bristol.

Mr. MENDELSOHN. That is correct.

Mr. DEUTSCH. That would put your total of ImClone holding at about $30 million at the time; is that correct?

Mr. MENDELSOHN. At the value of $70, that is correct. Yes.

Mr. DEUTSCH. Why did you not feel that your interest in ImClone was not significant enough to inform the M.D. Anderson patients enrolled in the Erbitux trials of that potential conflict?

Mr. MENDELSOHN. Right. Well, let me say that I am very conscious of conflict of interest and potential conflict of interest. From the point of view of conflict of interest, I have never treated a patient with C225. And I—from the point of view of potential conflict of interest, whenever I have given scientific talks or written papers or had public meetings, I have always stated my holdings in the company and my membership on its scientific advisory committee and on its board.

In November last year, before any of this happened, because of the concern I had about even a perception of conflict of interest, I instructed at M.D. Anderson that on all patient consent forms, my name be placed as a member of the board and holder of stock options at ImClone. This was done prior to the news article that has been referred to in these hearings from The Washington Post. And The Washington Post article acknowledges that in the article that I did do that.

I have bent over backwards to support research with any product that blocks the EGF receptor. I was contacted by AstraZeneka at M.D. Anderson and asked, would you be willing to study ERISA. I put them in contact with the same doctors that there were studying Erbitux. And in point of fact, there have been more studies of patients on ERISA at M.D. Anderson than with Erbitux.

So my goal is to get the patient the opportunity to have access to any drug that that particular patient and his or her physician feel has the best chance to help them.

Mr. DEUTSCH. I guess the focus though, is really on the issue of informed or—informed potential conflict, and the fact that the M.D. Anderson policy on disclosure would have seemed to require that disclosure when it was not.

Mr. MENDELSOHN. No. There were no requirements that the president disclose. I added that to our policies voluntarily. It is being discussed thoroughly. In the past 2 weeks, the American Association of Medical Colleges has put out guidelines, which I am reading carefully. But I want to assure you that there was no policy at M.D. Anderson about this. When I came to M.D. Anderson, I put in a policy that no one who has a vested interest in experimental drug can treat a patient with that drug. That was novel then. This was something that I did on my own initiative at M.D. Anderson.

Mr. DEUTSCH. So I guess the bottom line of your testimony to this point is that you felt there was no conflict in terms of the disclosure requirement on any outside standards?

Mr. MENDELSOHN. I believed that. But I also was concerned enough about the potential perception of conflict of interest that I

added that. I regret that I didn't do that at the very beginning when all of this started. But I added that to our procedures at M.D. Anderson without prompting and of my own volition.

Mr. DEUTSCH. One of the continuing trends or questions that we have asked and that has been going on is really the independence and diligence of outside directors which shareholders must rely upon to keep management honest and protect the interest of important corporate decisions.

You serve or served on both the ImClone board and Enron, obviously two firms whose shareholders have taken a great deal of financial adverse effect, while very well compensated managers have been charged with crimes involving their fiduciary duty.

Would you tell us that you feel whether you did your job successfully, or did the management of these firms—what happened? Did the system fail?

Mr. MENDELSOHN. We are here, I believe, to talk about ImClone, and I believe that I have fulfilled my duties and that management has fulfilled its duties. Management has admitted in front of this subcommittee that there were aspects of the way that the registration clinical trial was carried out, which could have been done better. And we are hoping to have this ratified by the FDA after we hear from them the final details. But the answer to your question is, yes, I believe I have fulfilled all my duties.

Mr. GREENWOOD. Let me—while we await the return of other members, let me ask question of you, Dr. Waksal. I made reference to this article that was in the Wall Street Journal just a couple of weeks ago about, entitled "Four Prestigious Labs Ousted Waksal for Questionable Work."

Were you aware of these allegations?

Mr. WAKSAL. I was not.

Mr. GREENWOOD. Okay. When you were a resident at Tufts New England Medical Center, did the chairman of the Department of Medicine, Sheldon Wolfe, complain to you about Sam Waksal, who was not a medical doctor, covering for you by seeing your patients at Tufts New England Medical Center?

Mr. WAKSAL. No, he did not.

Mr. GREENWOOD. You were not familiar with that allegation or concern at all?

Mr. WAKSAL. Well, I know that I was not there at the time. I do know that Dr. Sam Waksal, not masquerading as Harland Waksal, did speak to a patient that had been under my care.

Mr. GREENWOOD. Okay. Did ImClone have a succession plan for Sam Waksal? Address this to the board of directors.

Mr. GOLDHAMMER. We did not have a succession plan for Dr. Sam Waksal. Although, I personally thought that as the company got larger, that Sam would be inappropriate to have a large company because it just wasn't his style. He was wonderful with the young company, building a young company. The reason I had never really even thought serious about firing him along the way, A, because we never lost any money by any loans that we lent him or anything like that. He always paid it back. But he was the spirit for our young research group. And it is so important with a young company, you have just got to let them breathe. And he would do that and he would encourage them.

Mr. GREENWOOD. Would you ever consider him in the future as having a role at ImClone as an employee, as a director, as an officer, as a consultant, knowing what you know?

Mr. GOLDHAMMER. I would consider having him a consulting something if he so desired. I doubt if he would do it.

Mr. GREENWOOD. Okay.

Mr. GOLDHAMMER. He would be excellent.

Mr. GREENWOOD. Even if he is convicted?

Mr. GOLDHAMMER. Oh, no, no, no. But he would be an excellent consultant, is what I meant.

Mr. GREENWOOD. Would you, Mr. Goldhammer, describe the membership and purpose of the executive committee at ImClone.

Mr. GOLDHAMMER. Well, the membership today at ImClone is, the executive committee has three outside board members and Harlan.

Mr. GREENWOOD. What was it last year?

Mr. GOLDHAMMER. Before we changed it, it was myself and Harlan. And while Sam was here, he was on it, although we didn't have any meetings.

Mr. GREENWOOD. According to the bylaws of ImClone, which are in Tab 19 if you need to refer to them, actions by the executive committee must be ratified by the full board at the next meeting; is that right?

Mr. GOLDHAMMER. Yes.

Mr. GREENWOOD. Were all actions by the executive committee agreed to among yourselves, Sam and Harlan Waksal put to the board for approval?

Mr. GOLDHAMMER. I believe so.

Mr. GREENWOOD. You have acted as a director on the boards of Kidder, Peabody and Company, the Boston Stock Exchange, Eastern Line Corporation, and Community Connected, Incorporated. Was it ever the practice of the executive committees of those firms to act without eventual reporting and approval by the full boards?

Mr. GOLDHAMMER. No.

Mr. GREENWOOD. Okay.

Mr. GOLDHAMMER. Some of the young ones don't really have an executive committee.

Mr. GREENWOOD. But where there are executive committees, they always reported to the boards.

And let me ask Mr. Kopperl and Mr. Mendelsohn, as members of the board, were you given minutes and documents of all meetings or decisions by the executive committee?

Mr. KOPPERL. I don't believe that we—I do not believe that we were given minutes of the executive committee meetings.

Mr. GREENWOOD. Okay. Did you and the board ratify all actions of the executive committee?

Mr. KOPPERL. I do not recall specific instances, Mr. Greenwood. However——

Mr. GREENWOOD. Let me give you some specific instances. In January 1998, a loan in the form of a promissory note to Sam Waksal in the amount of 100—nearly $130,000. Did you approve that?

Mr. KOPPERL. I do not recall.

Mr. GREENWOOD. Okay. That is at Tab 4. In October 1998, a loan in the form of a promissory note to Sam Waksal in the amount of $100,000. That is in Tab 6.

Mr. KOPPERL. I do not recall whether the board ratified that. We would have to look at the minutes, obviously, of the board.

Mr. GREENWOOD. Okay. And February 2001, a loan in the form of a promissory note to Sam Waksal in the amount of $282,200.

Mr. KOPPERL. That was indeed ratified by the board.

Mr. GREENWOOD. That one was. Well, you are one for—you can remember one for four. In August 2001, an extension of the February loan of $282,200 to Sam Waksal for another 4 months. Were you aware of that?

Mr. KOPPERL. I am certainly aware of that. And indeed, the audit committee on October 10, 2001 took up the issue of the $282,200 loan and questioned the documentation of this loan. However, I would add that the loan was repaid in full with interest, I believe, on November—in mid November 2001.

Mr. GREENWOOD. Okay. Dr. Mendelsohn, have you ever attended one of ImClone's EGFR, epidermal growth factory receptor summits?

Mr. MENDELSOHN. Yes.

Mr. GREENWOOD. Where and when did you attend that?

Mr. MENDELSOHN. There were a number of them. Yes, I have attended a number of them, probably most that they had. So the answer would be yes. But I don't remember the locations.

Mr. GREENWOOD. How about Cancun, Mexico in the winter of 2000?

Mr. MENDELSOHN. Yes.

Mr. GREENWOOD. Who paid for this program?

Mr. MENDELSOHN. ImClone.

Mr. GREENWOOD. Mr. Landes, did you ever perform legal work for another company while at ImClone?

Mr. LANDES. There were such occasions, yes.

Mr. GREENWOOD. What was the nature of this work?

Mr. LANDES. There was a company called Tribeca that—for which a license was given from the University of Chicago. I was involved in helping that company obtain that license. Very little time was spent, but it was within my expertise. And that was a company that I expected, and still may be the case, might have some scientific synergy between its work and that of ImClone.

Mr. GREENWOOD. And who paid your fees for that service, that work?

Mr. LANDES. As I recall, I received—I did receive a small fee for that I believe from the Tribeca company. But again, that—I don't think that fee necessarily represented the compensation entirely for the work. Again, this was something that I believed would have potential synergy between——

Mr. GREENWOOD. Is it fair to say that ImClone paid you to do that work?

Mr. LANDES. Mr. Chairman, I think it is possible that one could take that view, at least a portion of that. Yes.

Mr. GREENWOOD. And Sam Waksal, that was Sam Waksal's company; correct?

Mr. LANDES. I don't really know the nature of the ownership of Tribeca. I knew that Sam was involved. And Sam had also again explained to me his concept, which I thought and still think was a valid one, that there would be synergies between a company like that, which was working in the area of herpes simplex infectious diseases and our work in cancer.

Mr. GREENWOOD. Mr. Landes, who at ImClone cleared your carry forward sales transaction of $2.5 million worth of ImClone stock on December 6 of last year?

Mr. LANDES. That was cleared by Cathy Vaczy.

Mr. GREENWOOD. Was she your subordinate?

Mr. LANDES. She worked in my department and I supervised the department. Yes.

Mr. GREENWOOD. Did you see any problem with your support and it being able to clear your trade?

Mr. LANDES. I did not.

Mr. GREENWOOD. If you made such a trade now, who would clear the trade?

Mr. LANDES. Now, it would be cleared by Daniel S. Lynch, who is the chief financial officer of ImClone.

Mr. GREENWOOD. And why was the policy changed in that regard? Maybe I should ask Mr. Kopperl that question.

Mr. KOPPERL. I believe that it would be Mr. Saffron, who would approve or disapprove any such.

Mr. GREENWOOD. Is he the CFO?

Mr. KOPPERL. No. He is senior vice president and general counsel.

Mr. GREENWOOD. So why did you make that change?

Mr. KOPPERL. We made the change because in—I forget, was it February or March of this year—we determined that the insider trading procedures, which were in place and which everyone is aware of, needed to be strengthened. And this—perhaps it was even later than that, Mr. Greenwood, because it may have been shortly before the Oxley-Sarbanes bill or law, that we determined that there would be a new, more rigid procedure followed.

Mr. GREENWOOD. Ms. Vaczy, at the time, did you see any impropriety with you approving the transaction for your superior?

Ms. VACZY. I did not.

Mr. GREENWOOD. Okay. And what is your understanding right now as to who would clear such a transaction under the current regime?

Ms. VACZY. Clear transaction by Mr. Landes?

Mr. GREENWOOD. Right.

Ms. VACZY. It would be done by Mr. Lynch, who is our CFO. The structure under the revised policy are members of the legal department are approved by the CFO.

Mr. GREENWOOD. So we just had a different answer from Mr. Kopperl. So——

Mr. KOPPERL. I defer to them, as to the legal department, sir.

Mr. GREENWOOD. Okay.

Dr. Waksal, who was Sonya Benahutta?

Mr. WAKSAL. I believe she is a friend of Sam Waksal's.

Mr. GREENWOOD. Okay. If you turn to Tab 60, according to a September 30, 2002, letter from Omelvani and Meyers, Sonya

Benahutta was not an employee at ImClone, and yet ImClone has produced records of a cell phone paid by ImClone, but used by Ms. Benahutta in addition to e-mails have been produced showing Ms. Benahutta as being on the ImClone e-mail system. Can you explain why a non-employee at ImClone would have use of an ImClone cell phone and have access to internal ImClone e-mail?

Mr. WAKSAL. I know nothing about this.

Mr. GREENWOOD. Do you know—so you don't even know if it is still the case that that—that these things are happening?

Mr. WAKSAL. I do know that it came to my attention that she had been on ImClone's e-mail system. It was brought to my attention by the systems people. And my understanding is that she was——

Mr. GREENWOOD. When was that?

Mr. WAKSAL. That was about I guess 3 or 4 weeks ago. And from what I understand, she is—and I can't—I really would have to get back with you, but I do not believe she is on the system. When it was brought to my attention, I expressed——

Mr. GREENWOOD. Did she receive any other benefits or compensation from the company, that you were aware of?

Mr. WAKSAL. She was not involved with ImClone Systems.

Mr. GREENWOOD. But that was not exactly my question.

Mr. WAKSAL. Not to my knowledge, sir.

Mr. GREENWOOD. Thank you.

The gentlelady from Colorado is recognized for 10 minutes.

Ms. DEGETTE. Thank you, Mr. Chairman.

Ms. Vaczy, when did ImClone begin to be aware that the FDA may—that there may have been some issues with the FDA removing Erbitux from consideration?

Ms. VACZY. As I said earlier, and I believe we discussed in the last hearing, it was December 12, Dr. Lee had a conversation with the FDA where minutes of that conversation reflect her concern regarding their change of tone.

Ms. DEGETTE. And when did you become aware that the—was it around December 12 that you became aware of that issue?

Ms. VACZY. I attended a meeting on December 12, and I had heard about the meeting the evening of December 11 that we were going to discuss after the company's—the management operations meeting an issue relating to the BLA.

Ms. DEGETTE. Now, at that point—do you know—do you know, were others at ImClone aware of FDA concerns before December 12? Did anybody tell you about that?

Ms. VACZY. December 12 was the first contact that I am reporting, and it is not I who have the direct contact with the FDA. But per Dr. Lee, who was the main communicator, the conversation she had on December 12 was the first time she was concerned that there might be issues with the acceptance of the filing.

Ms. DEGETTE. And you imposed a blackout period for the sale of ImClone stock by insiders on December 21 of that year; correct?

Ms. VACZY. Well, it was a blackout companywide. On the 18th of December, we started precluding members of management trading. But we also, during that interim, December 12 to 18, we relied on the fact that the select members of management that had knowledge could not proceed with any transaction without first being——

Ms. DEGETTE. But there was no—do you have a written policy as of the December 18 of the blackout policy? Because just now today is the first I have ever heard of it as of that date.

Ms. VACZY. There was an e-mail on December 18 to members of management.

Ms. DEGETTE. From you?

Ms. VACZY. Yes.

Ms. DEGETTE. And what did it say?

Ms. VACZY. I think I have seen it——

Ms. DEGETTE. Do you have a copy of it?

Ms. VACZY. I may have seen it in your exhibits, I believe, if I am not mistaken. But I don't recall.

Ms. DEGETTE. Mr. Chairman, if we can ask permission for Ms. Vaczy to find that memo, I think that would be very helpful.

Mr. GREENWOOD. Perhaps have you found it? Tab 21. Try Tab 21.

Ms. VACZY. I may be mistaken.

Ms. DEGETTE. Yeah. Because we don't have——

Ms. VACZY. But I can nonetheless speak to it.

Okay. I am advised I was shown it during my interview where counsel is reminding me, and we are obtaining it now.

Ms. DEGETTE. Okay. We have not been produced any evidence of a written blackout policy before December 21. So, Mr. Chairman, if that is the case, I would ask this witness to produce that policy for our committee.

Ms. VACZY. It has been suggested that I read the Bates ranges of two documents in front of me. HCEC-30479, and 78. Well, no, I am sorry, not 78. 79—and HCEC-30496. And I think maybe I am perhaps confusing you. On the 18th, an e-mail was sent to members of management reminding them that they were required to get preapproval of any transaction from the legal department under the insider trading policy.

Ms. DEGETTE. So, in fact, you did not impose a blackout period on the 18th; you imposed it on the 21st?

Ms. VACZY. Well, no. If I can——

Ms. DEGETTE. Well, really, that is true. On the 18th, you said if you want to sell your stock, you have got to get preapproval.

Ms. VACZY. Yes. But then we had, I think, perhaps three members of management who contacted us and we said no.

Ms. DEGETTE. Oh. Who contacted you? And during what time period?

Ms. VACZY. There were members of management on the 18th who said would we be permitted to sell stock.

Ms. DEGETTE. Who was that?

Ms. VACZY. Let us see. I recall one gentleman, Gary Palter, who is a member of our management.

Ms. DEGETTE. Was he aware of the FDA concerns?

Ms. VACZY. He was not——

Ms. DEGETTE. As of the 18th?

Ms. VACZY. To my knowledge, no, he was not in the group of members of management.

Ms. DEGETTE. He just happened to ask you could he sell his stock?

Ms. VACZY. We would ask have to ask Gary, but I believe so.

Ms. DEGETTE. Well, I am asking you what he asked you.

Ms. VACZY. He said would—and it is not in this e-mail, and I am just trying to recall.

Ms. DEGETTE. Sometimes people have independent recollections, too, from e-mails. So that is what I am asking for.

Ms. VACZY. Okay. After sending the e-mail on the 18th, reminding management——

Ms. DEGETTE. That they had to check with you?

Ms. VACZY. That is right.

Ms. DEGETTE. Okay. Then he called you.

Ms. VACZY. Yes.

Ms. DEGETTE. Who else called you?

Ms. VACZY. I don't—I don't recall.

Ms. DEGETTE. You said three members.

Ms. VACZY. Yeah. I remember there were three people, but I don't remember necessarily who they were.

Ms. DEGETTE. Okay. If you could look at Tab 19 in your notebook. That is the ImClone Systems, Incorporated Board of Directors Handbook. Are you familiar with that——

Ms. VACZY. I am.

Ms. DEGETTE. [continuing] document?

Ms. VACZY. Yes, I am.

Ms. DEGETTE. Okay. If you could look at page 21 of that document.

Ms. VACZY. Yes.

Ms. DEGETTE. Okay. And D says: "there will be periods of time when it is clear that material non-public information is known by several employees, officers, and directors of the company." And then it goes on to say there would be a blackout period when that happens. Are you familiar with that policy?

Ms. VACZY. I am.

Ms. DEGETTE. Now, wouldn't it be the case that a blackout period should have been imposed from December 12 on, since at that time there was knowledge of material non-public information?

Ms. VACZY. Congressman, we looked at this very carefully during this entire period. And our feeling was, no, not until the communication on December 20 was it appropriate to put in place a companywide blackout.

Ms. DEGETTE. Well, then why did you, on the 18th, tell people they couldn't sell their stock?

Ms. VACZY. It wasn't people in general. It was members of management.

Ms. DEGETTE. Okay. Well, why did you tell members of management that if you feel you didn't have to impose the blackout period until the 20th of December?

Ms. VACZY. It was our feeling that management, being members of management, they are held to a higher standard. And we didn't feel it was appropriate at that time that management be trading.

Ms. DEGETTE. But see, that is not what the company policy says. Is it? I mean, the company policy says whenever there is material non-public information, then everybody is in the blackout period.

Ms. VACZY. We didn't consider it to be material non-public information.

Ms. DEGETTE. If you take a look—yeah. Who is "we"? Who is "we didn't consider it to be material"?

Ms. VACZY. Management of the company. We——

Ms. DEGETTE. Who in management?

Ms. VACZY. We—it would be our management group, our COO or CEO or CFO.

Ms. DEGETTE. Who did you discuss the decision with to impose—to send out the memo on the 18th and then to impose the blackout period?

Ms. VACZY. On each—in each of these situations, we were discussing this all along during this period with our outside counsel. And I recall, it was Harlan Waksal and Dan Lynch who—and I believe Sam Waksal was involved in the 18th, and then on the 20th it was Dan lynch and Harlan Waksal who——

Ms. DEGETTE. Who from your outside counsel did you discuss this with?

Ms. VACZY. We were discussing with our FDA counsel and with our securities counsel.

Ms. DEGETTE. All right. If you will take a look at Exhibit 1 in the notebook, ImClone officer stock sales. It looks to me like there were nine sales of stock between—eight sales of stock between the December 12 and December 21.

Ms. VACZY. Are you looking on the third page?

Ms. DEGETTE. Well, I am going to go back to something else. I have been given the wrong number.

I just want to ask you a question, Dr. Mendelsohn. You had told Mr. Deutsch that you recommended implementing a conflict of interest policy at M.D. Anderson. And I guess I just wanted to know when you recommended that.

Mr. MENDELSOHN. There have been a number of stages. Right after I came there, I recommended a new policy that anyone——

Ms. DEGETTE. When was that?

Mr. MENDELSOHN. 1996.

Ms. DEGETTE. Okay.

Mr. MENDELSOHN. So I think it went into effect in 1997, that anyone who had a potential financial interest in an investigational drug could not administrator that to a patient and could not be the principal investigator in a trial of it.

Ms. DEGETTE. And I think that is great. But I also, see—you probably know this. I am trying to do legislation. I have introduced legislation for even broader disclosure than that, because it seems to me someone like you who is a very, you know, fine scientist and really trying to do this, but anyone involved with the research institution that is doing clinical trials, patients should have informed consent of that conflict.

Mr. MENDELSOHN. Right. We—I agree with that statement, and in November 2001, prior to the article in the Washington Post and prior to the recent reports that have come out with recommendations, I instituted a policy at M.D. Anderson that my name would go on all clinical trials involving Erbitux.

Ms. DEGETTE. And, in fact, in January 2001, prior to that, the Office for Human Research Protections recommended that you implement such a policy, correct?

Mr. MENDELSOHN. The Office of Human Research Protection—the director of that office actually visited us at M.D. Anderson, and we discussed these issues.

Ms. DEGETTE. Right.

Mr. MENDELSOHN. At that time it was recommended that we consider this kind of thing.

Ms. DEGETTE. And that was after the Erbitux study was completed, right?

Mr. MENDELSOHN. That was after most of it had been completed.

Which study are you referring to? Because the Erbitux study that was the study—that was the registration study, M.D. Anderson did not participate. We didn't participate in that study at all.

Ms. DEGETTE. Right. I just have one last question for you.

At the last hearing we—and I know some of the other members have touched on this a little bit, but at the last hearing we talked about the thousands of colorectal cancer patients who really had hope in Erbitux, and I guess I would just ask you if you could very briefly tell us, now that the FDA has taken the drug off of the fast-track approval list and all of these questions have been raised not just about the corporate improprieties, but also the research protocols and the clinical trials, my question to you is, what is ImClone doing to try to get that drug back on track with the research?

Are you doing new trials, and what is your timeframe for that?

Mr. MENDELSOHN. I can give you some answers to that, and maybe Dr. Waksal can add.

First of all, I believe we are still on the fast-track list, but they have not accepted our BLA, obviously. We are meeting with the FDA to try to find out exactly the criteria we should use, because we want to look at the data on that trial again. We believe that many of the issues that have been raised in the press are not relevant to that trial.

Excellent investigators from many institutions stand by these data, and we want to have it reviewed in the way the FDA wants it, so it is reported and documented properly. Then ImClone is planning with its partner, Bristol, a large number of additional trials that are answering all the questions that have been raised, I believe. So we are very——

Ms. DEGETTE. Quickly, what is your timeframe for all of this?

Mr. MENDELSOHN. It depends which trials the FDA accepts. It could be—it could be a year. It could be 2 or 3.

Ms. DEGETTE. Thank you. Thank you, Mr. Chairman.

Mr. GREENWOOD. The time of the gentlelady has expired.

Just a couple questions for myself and then I am going to turn it over to Dr. Fletcher to close the hearing.

Dr. Waksal, at Tab 24 you will see a letter dated September 13, 2002, from O'Melveny & Myers to this committee, regarding the purchase of shredders in January 2002, an e-mail of January 7 between Sam's assistant and your assistant and the purchase order, which you signed.

The letter says that you played no role in the decision to purchase the shredders other than signing a routine purchase order, the contents of which you did not review.

Is it your practice to sign purchase orders without reviewing their contents?

Mr. WAKSAL. It is my practice to review contents of purchase orders unless those purchase orders don't strike me and don't hit my attention that strongly. This was a purchase order of a relatively low amount of money, but most importantly, aside from the fact that they are shredders, as I have sent into this committee and certified, I did not at any time destroy any documents, nor did I instruct anybody to destroy documents, nor am I aware of anyone in the company destroying documents that are subject to any investigations that are taking place, other than what has been attributed to Dr. Sam Waksal.

Mr. GREENWOOD. When you said you review purchase orders, and you sometimes, when something strikes you as seeming—did you know that you signed an order to purchase shredders?

Mr. WAKSAL. As I have said, and I am embarrassed to say this, I don't remember this purchase order, and I am very clear on how that appears.

The purchase of shredders gives an impression that during this period of time that there may be some motivation to do so.

I have to say, there were shredders at the company and in all of our facilities already only 100 yards away from my office, and as I said, no shredder was used by me or anybody under my direction or anyone in the company to destroy or affect any documents that were relevant to any investigation.

Mr. GREENWOOD. According to Sam Waksal's message log, you received a phone call from an SEC investigator on January 3, 2002. When did you first become aware that Sam had been called by the SEC?

Mr. WAKSAL. I wasn't aware of that call, but I did know sometime around the 8th, around January 8, that indeed the SEC was making inquiries.

Mr. GREENWOOD. Do you know now what inspired the preparation of a purchase order for shredders? Did you look back and say, whose idea was it to get shredders, and why, since you didn't see them—you say you didn't see that at the time?

Mr. WAKSAL. Of course we have gone ahead and investigated this, and that is right—part of the documentation that was sent over to your office.

Indeed, what was explained to me is that the administrative assistants were—felt that it would be good for them to have a shredder in a conference room close by their areas of work. It was in conjunction with routine practice, and it certainly wasn't anything extraordinary to them. At the time, the investigations were just early inquiries, and I don't believe there was any motive other than what, in their minds, was normal work activity.

Mr. GREENWOOD. Just bear with us for a moment.

Mr. FLETCHER [presiding]. Again, I want to thank the chairman for conducting this hearing. I have got a few questions I would like to do in closing out.

Let me ask, Dr. Mendelsohn, what is the incidence of colon cancer in the country at this time, or what do you expect it to be in the future?

Mr. MENDELSOHN. As I remember, well over 100,000 cases a year, and I expect it to go down, because if Americans all underwent colonoscopy, as recommended, the death rate would go down

substantially; the incidence of disease would probably go up, we would pick it up early, but the death rate would go down.

Mr. FLETCHER. There are some that estimate that, you know, the incidence may double over the next 50 years. I am not sure how they——

Mr. MENDELSOHN. That is correct. It is very interesting. It is a demography issue. We are an aging population, so that even though the risk of dying from many cancers has gone down because they are just diagnosed earlier and the therapy is better, because there are so many more older people, the incidence of the disease is going up, and that will continue until 2025, as I understand it, when the baby boom gets finished.

Mr. FLETCHER. Probably most families, directly or indirectly, have been affected by colon cancer, and let me ask you, there's a reported 22 percent response, and these are the most complicated recalcitrant cancers that were tested. So would you say that the response rate to other cancers that were not so recalcitrant might be higher, or would you estimate that? Is there hope that that might be the case?

Mr. MENDELSOHN. There certainly is hope, and there's a hope that if we treated the colon cancer patients earlier with chemotherapy, not with a drug they had already shown resistance to, that we would get a better response, but this will all have to be tested in clinical trials.

Mr. FLETCHER. Let me ask you—and maybe I will ask Mr. Goldhammer this.

What were y'all's calculations when you based the return on Erbitux of the projected rate of income, if you will, with the treatment of colon cancer, considering that the incidence, or rate, is going up because of the demographic changes that Dr. Mendelsohn described, as well as the possibility of using this not only in the recalcitrant cases, but earlier in the diagnosis of colon cancer?

Did you y'all have numbers that you projected on the sales?

Mr. GOLDHAMMER. Yes, we did.

Mr. FLETCHER. Could you share those with us? What were your projected sales over the next 5 or 10 years?

Mr. GOLDHAMMER. I will do it roughly, but I might be able to send it to your office.

Mr. FLETCHER. Well, we would appreciate it if you would submit those, but can you give us a rough estimate?

Mr. GOLDHAMMER. Yeah. I think that we thought that year 1, for instance, we might have in a launch—$60 million or so in sales. We thought the next year would be $100 million and—Harlan, help me a little bit.

Mr. WAKSAL. If I can, our estimates ranged from $300 million to $1 billion over the course of about a 5-year period of time.

Mr. FLETCHER. So tremendous potential financially, and obviously there has been a lot of money that was invested in developing the drug; and Dr. Mendelsohn, I know you were very early in developing C225.

Let me get back to the science. Let me say from my standpoint, you know, the Justice Department can take care of some of the other things. I am concerned of the fact that we have a drug, I think, that is still very promising. There are people out there not

getting that because of some mistakes made, or at least it appears that way to me.

Here in Tab 35, dated March 25, 2002, the FDA in their presentation in the first—it starts, "The following captures the discussion that occurred during the FDA's presentation." This was a meeting regarding ImClone, regarding the study—refusal-to-file letter issued to their BLA for Erbitux.

It says, "The FDA clearly stated to ImClone that the reanalysis of the data from this study"—and it is CPO 29923—"will not be sufficient to address the deficiencies in this application. This conclusion is based upon a determination that there are significant design and conduct flaws in the study that cannot be fully addressed by sending missing data. Data from an additional trial or trials that are adequate and well controlled are necessary."

And yet, in my last line of questioning, Dr. Waksal, you seemed to insist that it was sound science, that the study was good.

Now, let me ask you. I only see three options here: Either you all or some of you there were asleep at the wheel and not realizing what was going on; two, you don't—either that or you don't recognize what sound science is; or three, the FDA doesn't recognize what sound science is. Because we have quite a contradiction here.

I wonder if you could help me out. Which one of those is the situation in your conclusion?

Mr. WAKSAL. I think it is D, none of the above.

Mr. FLETCHER. I thought it might be that.

Mr. WAKSAL. Look, there is no question, as I reported at the last session—the last time I was here, 4 months ago; and hopefully I won't be back in another 4 months to talk about this.

However, I think what is really important, as I described, the study that was performed had deficiencies, deficiencies that we are trying to fix. However, at this stage we have not said that once we fix the deficiencies of that trial, that that trial will now be sufficient to move forward.

The world has changed. There have been a number of issues that have come up that we need to attend to, and we stated at the last meeting, at the last congressional hearing that I attended, that ImClone would be looking to use a clinical development program that is a multifaceted program, using studies that are being done in Europe as a potential for working with our trial for approval and other trials in the U.S., as well. So we are not relying on that study at this stage.

Mr. FLETCHER. Well, what I think is clear from that—and I think the acknowledgment there is that you had a study whose protocol was somewhat flawed, even though you said it was designed by some of the leading experts in the field. You had the conduct of the study flawed, even in some of the leading institutions. You mentioned that you are a small company and probably oversight was not there, and yet you had the potential, it looked like, of making $300 million to $1 billion.

You know, one of the things we learn in medicine is that the most dangerous people are the people that don't know what they don't know.

Mr. WAKSAL. That is very true.

Mr. FLETCHER. And it disturbs me from that standpoint.

Let me get back to Dr. Sparling's letter. He said in his last paragraph of his letter dated January 15, "I know you are doing everything possible to get the drug filed and approved, and we are hoping this can be done as soon as possible for the sake of patients who need the drug."

And I commend Dr. Sparling, because I think his focus was appropriate.

The last sentence of his first paragraph in a letter dated February 21, it says, "I just do not believe I can be useful as a member of the SAB, the scientific advisory board, and the long-term inactivity of the SAB suggests the SAB is not useful to the company."

I will tell you, it has the appearance, the SAB, at least at this point—maybe early on, as Dr. Mendelsohn mentioned it was active, but—of being somewhat window dressing; and I don't know if there was a tremendous enthusiasm.

But I want to get to one last question, and this——

Mr. WAKSAL. If you don't mind, sir, if I can just address that. I think your point is a very important one.

Did the company use appropriate experts to help us and help guide us as we went forward? And I have to say, we did indeed. Members of the scientific advisory board were helping us in science, in basic research. The work we are doing clinically was done with oncologists, experts in the field, who were helping us as we went forward, and they had very different, distinct roles.

Mr. FLETCHER. And I understand that. I have been involved in some clinical studies and know that following the protocol is critical. Otherwise everything else doesn't count, because it has no credibility.

Dr. Waksal, let me ask you a question, and this is a different one. I want to ask you about a particular disturbing story that appeared in the press, which does make us question your motives in the development of Erbitux.

At Tab 49 you might see—you will see an article from the Atlantic Constitution entitled "Patients, a Low Priority for Drug Industry Leaders." It tells the story of Ruth Ann Santino, 51, a mother of two teenage sons and a woman fighting for her life against colorectal cancer, the target of ImClone's drug Erbitux.

At the advice of her doctor, she vigorously pursued Erbitux to the exclusion of other possible therapies on a compassionate-use basis. The CBS program 60 Minutes produced a piece on the availability of Erbitux, and Mrs. Santino was interviewed for the story. The allegation of the piece, as we understand it, was that the distribution of the drug to cancer patients was arbitrary and unfair.

I don't want to make any comment about the veracity of the allegations in the 60 Minute piece, but I do want to ask you about what you, Harlan Waksal, did in response to this program. Mrs. Santino's husband, Fred Santino, says that after the 60 Minute show aired and 2 days before Mrs. Santino died, you called the Santino home, raising hopes that ImClone might throw a lifeline to this woman and family in distress, but instead took to task Mr. Santino, whose wife was dying next to him, for being unfair to ImClone on 60 Minutes.

And to add insult to an unspeakable injury, you did not even ask about Mrs. Santino or offer her the use of the drug.

First, let me ask you, did you make that phone call?

Mr. WAKSAL. Yes, I did, but the call was not made to take issue with Mr. Santino. In fact, my call was made in a response to the fact that I wanted to correct some points on record. I wanted him to know that, indeed, we were doing nothing to single out his family, his wife or patients who could not get access to our drug, but that there was not drug available under a compassionate-use program.

I didn't offer out hope. I offered what I believed was compassion and understanding that he was upset with the company, but I wanted him to know that the company was doing what we felt was right to get this drug approved and out there to patients like his wife.

Mr. FLETCHER. Did you offer the drug Erbitux to her? Did you have within the protocol of compassionate use, the power to offer that drug Erbitux?

Mr. WAKSAL. One, I did not offer the drug.

And second, the compassionate-use program had been stopped in January of that year. There was no compassionate-use program. There was no drug being used in compassionate-use studies other than patients already enrolled.

Mr. FLETCHER. Thank you. I think that concludes my questioning.

I appreciate all of you being here, and we will adjourn the meeting.

[Whereupon, at 4:16 p.m., the subcommittee was adjourned.]

[Additional material submitted for the record follows:]

Committee on Energy and Commerce
Subcommittee on Oversight and Investigations
An Inquiry into the ImClone Cancer-Drug Story, Day II
October 10, 2002

	Date	Document
1		**ImClone Personnel Stock Sales from 10/29/2001 - 12/31/2001**
2	4-Apr-91	Letters among Landes, Waksal, and Weiser - RE: Weiser stock purchase
3	28-Jun-93	*Barron's*: "Biotech CEO's Lifestyle Raises Investor Eyebrows"
4	23-Jan-98	Internal Memo - RE: S. Waksal Promissory Note (Exec. Cmte. Meeting Minutes)
5	12-Feb-98	ImClone Audit Committee Meeting Minutes
6	14-Oct-98	ImClone Executive Committee Meeting Minutes
7	2-Nov-98	ImClone Audit Committee Meeting Minutes
8	Jan-00	ImClone Annual Report
9	~Sept-00	Personal Notes
10	10-Nov-00	Letter to Bank of America - RE: Sam's stock pledge [faxed to Vaczy on 1/14/2002]
11	Jan-01	ImClone Annual Report
12	20-Feb-01	ImClone Special Executive Committee Meeting Minutes - RE: Loan to S. Waksal
13	23-Feb-01	John Mendelsohn's Director's Questionnaire
14	28-Mar-01	KPMG Report to ImClone Audit Committee
15	23-Apr-01	SEC Filing: Schedule 14A
16	10-May-01	ImClone Special Executive Committee Meeting Minutes - RE: Loan to ACT Group
17	18-Jul-01	ImClone BOD Special Telephonic Meeting Minutes
18	7-Aug-01	ImClone Special Executive Committee Meeting Minutes - RE: Loan to S. Waksal
19	Sep-01	ImClone BOD Handbook
20	18-Dec-01	Thomas Gallagher e-mail - RE: Exercise of Options & Sale
21	21-Dec-01	Cathy Vaczy e-mail - RE: company-wide black-out in trading ImClone stock
22	21-Dec-01	Michael Needle e-mail - RE: Final draft of 9923 paper
23	Jan-02	ImClone Annual Report
24	7-Jan-02	Emily Perret e-mail - RE: "Sam needs a paper shredder" [w/ expl. from O'Melveny]
25	15-Jan-02	Letter to Waksals from UNC medical professor - RE: SAB, post-RTF letter
26	18-Jan-02	Letter to Waksals from Bank of America SVP - RE: Loan Default
27	25-Jan-02	ImClone BOD Special Meeting Minutes
28	29-Jan-02	*WSJ*: "ImClone Directors had Contracts with Firm Worth $112,000 a Year"
29	8-Feb-02	E-mail to David Kies - RE: Charitable Contributions since 1-Jan-99
30	21-Feb-02	Letter to Waksals from UNC medical professor - RE: Resignation from SAB
31	22-Feb-02	*WSJ*: "ImClone CEO Returns $486,000 Profit....."
32	27-Feb-02	John Mendelsohn's Director's Questionnaire

Committee on Energy and Commerce
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33	19-Mar-02	ImClone Compensation & Stock Option Cmte. Meeting Minutes
34	25-Mar-02	Letter from H. Waksal to UNC professor - RE: Proffessor's SAB resignation
35	25-Mar-02	FDA Letter - RE: 2/26/02 meeting with ImClone regarding RTF letter
36	26-Mar-02	*Reuters*: "ImClone's CEO violates SEC rules with stock filing"
37	28-Mar-02	Personal Note from Richard Barth to Chairman of the Board, R. Goldhammer
38	29-Mar-02	*WSJ*: "ImClone CEO's Transaction Reports are Late"
39	29-Mar-02	ImClone BOD Meeting Minutes
40	2-Apr-02	Personal Note from Richard Barth to Chairman of the Board, R. Goldhammer
41	15-Apr-02	*Fortune*: "The Socialite Scientist"
42	24-Apr-02	SEC Filing: Schedule 14A
43	25-Apr-02	Internal Memo from Clifford Saffron - RE: New Insider Trading Policy
44	11-Jun-02	*United States of America v. Samuel Waksal*, Southern District of New York
45	14-Jun-02	E-mail from Fred Santino - RE: ImClone & his wife's "60 Minutes" story
46	19-Jun-02	ImClone Press Release - RE: Receipt of SEC "Wells Notice"
47	27-Jun-02	Letter to Deputy Comm. Crawford - RE: Fast-track Drug Approval Process
48	30-Jun-02	*Washington Post*: "A Hospital's Conflict of Interest; Patients Weren't Told...."
49	5-Jul-02	*Atl. Journal Constitution*: "Patients a Low Priority for Drug Industry Leaders"
50	7-Aug-02	*United States of America v. Samuel Waksal*, Grand Jury
51	14-Aug-02	*ImClone Systems Inc. v. Samuel D. Waksal*, Supreme Court of NY
52	29-Aug-02	John Jenkins e-mail - RE: Communictions Policy, re: Review of INDs & NDAs
53	29-Aug-02	*Peer View Press*: "Monoclonal Antibodies Targeting the EGF Receptor...."
54	1-Sep-02	*Journal of Clinical Oncology*: Colorectal Cancer Patients
55	12-Sep-02	*WSJ*: "To Outsiders, Insider Choices Don't Add Up"
56	18-Sep-02	E-mail from Paul Gluckow - RE: Questions on submitted documents
57	25-Sep-02	*PR Newswire*: "Biotech CEOs Average $513,000; Waksal's Most Lucrative.."
58	27-Sep-02	*WSJ*: "At Four Prestigious Labs, ImClone Founder Faced Questions....."
59	30-Sep-02	Letter to Dr. Crawford - RE: Drug Approval, Communicating with Companies
60	30-Sep-02	Letter from ImClone attys. - RE: Documents, re: Loan to ACT Group, Inc.
61	4-Oct-02	*WSJ*: "Whither Erbitux? For Dying Patients, Time is Running Out"
62	4-Oct-02	*Washington Post*: "ImClone Resumes Tests of Cancer Drug Erbitux"
63	6-Oct-02	Letter from ImClone attys. - RE: Loans to Samuel D. Waksal
64	7-Oct-02	*Dow Jones Business News*: "Boards Need More Women....."

ImClone Personnel Stock Sales
10/29/2001 - 12/31/2001

	December 2001*	**10/29 - 12/31***
Directors	$57,038,974	$204,915,234
Officers	$13,349,394	$35,678,219
Employees	$3,418,313	$3,418,313
Total	$73,806,681	$244,011,766

* Please see subsequent charts for explanation of price determination

ImClone Directors' Stock Sales
10/29/2001 - 12/31/2001

Director	Title	Date	Transaction Type	Shares	Price*
Richard Barth	Director	10/29/2001	Option Exercise & Same Day Sale	27,328	$1,912,960
		12/12/2001	Option Exercise & Same Day Sale	2,500	$172,190
				Barth Total:	**$2,085,150**
Vincent Devita, Jr.	Director	10/29/2001	Sale	129	**$9,030**
Robert Goldhammer	Director	10/29/2001	Sale	364,781	**$25,534,670**
David Kies	Director	10/29/2001	Sale	30,007	$2,100,490
		12/14/2001	Gift	30,000	$2,100,000
				Kies Total:	**$4,200,490**
Paul Kopperl	Director	10/29/2001	Option Exercise & Same Day Sale	6,430	$450,100
		10/29/2001	Sale	21,434	$1,500,380
				Kopperl Total:	**$1,950,480**
Arnold Levine	Director	10/29/2001	Sale	1,329	**$93,030**
John Mendelsohn	Director	10/29/2001	Option Exercise & Same Day Sale	90,226	**$6,315,820**
William Miller	Director	10/29/2001	Sale	8,573	**$600,110**
Harlan Waksal	Director, CEO (Former COO)	10/29/2001	Sale	777,607	$54,432,490
		12/6/2001	Forward Sale Agreement	700,000	$50,358,000
				H. Waksal Total:	**$104,790,490**
Samuel Waksal	Director, Former Pres. & CEO	10/29/2001	Sale	814,674	$57,027,180
		12/28/2001	Gift	79,797	$4,408,784
				S. Waksal Total:	**$61,435,964**
				Director Total:	**$204,915,234**

* Prices exact, except for "Gift" transactions (estimated using closing share price on day of transaction)

ImClone Officers' Stock Sales
10/29/2001 - 12/31/2001

Officer	Title	Date	Transaction Type	Shares	Price (Approx.)*
Michael Bailey	AVP, Marketing (as of 1/02)	12/21/2001	Sale	3,400	**$214,064**
Peter Bohlen	Senior VP, Research	10/29/2001	Option Exercise & Same Day Sale	46,833	$3,278,310
		11/7/2001	Sale	424	$26,305
				Bohlen Total:	**$3,304,615**
Lisa Cammy	AVP, Human Resources	10/29/2001	Option Exercise & Same Day Sale	4,287	$300,090
		11/2/2001	Sale	2,454	$152,246
		12/14/2001	Sale	3,500	$245,000
		12/17/2001	Sale	4,500	$308,745
		12/18/2001	Sale	996	$65,487
				Cammy Total:	**$1,071,568**
Richard Crowley	VP, Manufacturing & GM	10/29/2001	Option Exercise & Same Day Sale	3,215	$225,050
		11/27/2001	Option Exercise & Same Day Sale	4,000	$282,600
				Crowley Total:	**$507,650**
Charles Dunne	VP, Systems & Facilities	10/29/2001	Option Exercise & Same Day Sale	8,788	$615,160
		11/2/2001	Sale	10,717	$664,883
		12/13/2001	Sale	5,000	$348,050
		12/14/2001	Option Exercise & Same Day Sale	32,212	$2,254,840
				Dunne Total:	**$3,882,933**
Thomas Gallagher	VP, Intellectual Property	10/29/2001	Option Exercise & Same Day Sale	11,949	$836,430
		12/14/2001	Option Exercise & Same Day Sale	20,000	$1,400,000
				Gallagher Total:	**$2,236,430**
Paul Goldstein	VP, Financial Operations	10/29/2001	Option Exercise & Same Day Sale	8,573	$600,110
		11/2/2001	Sale	4,501	$279,242
		11/20/2001	Gift	200	$13,412
		11/27/2001	Option Exercise & Same Day Sale	9,000	$635,850
				Goldstein Total:	**$1,528,614**
Daniel Hicklin	AVP, Immunology	11/13/2001	Sale (Call Contracts)	10,000	$623,800
		11/19/2001	Sale (Call Contracts)	2,200	$150,590
		12/3/2001	Sale (Call Contracts)	10,000	$712,500
		12/6/2001	Sale (Call Contracts)	30,000	$2,158,200
		12/17/2001	Sale (Put Contracts)	5,000	$343,050

* Estimated using closing share price on day of transaction, except for 10/29 sales (Tender Offer)

ImClone Officers' Stock Sales
10/29/2001 - 12/31/2001

				Hicklin Total:	**$3,988,140**
John Landes	Senior VP, Legal	10/29/2001	Option Exercise & Same Day Sale	37,871	$2,650,970
		10/29/2001	Sale	47,272	$3,309,040
		12/6/2001	Forward Sale Agreement	40,000	$2,877,600
				Landes Total:	**$8,837,610**
Ronald Martell	VP, Sales & Marketing	10/29/2001	Option Exercise & Same Day Sale	6,507	$455,490
		11/2/2001	Sale	9,645	$598,376
		12/10/2001	Forward Sale Agreement	35,355	$2,483,689
				Martell Total:	**$3,537,555**
Nikhil Mehta	AVP, Regulatory Affairs	11/2/2001	Sale	331	$20,535
		12/11/2002	Sale	1,021	$71,868
		12/17/2001	Sale	192	$13,173
				Mehta Total:	**$105,577**
Michael Needle	VP, Clinical Affairs	10/29/2001	Option Exercise & Same Day Sale	5,358	$375,060
		11/26/2001	Option Exercise & Same Day Sale	19,642	$1,390,654
				Needle Total:	**$1,765,714**
Gary Paulter	VP, Engineering & Facilities	10/29/2001	Option Exercise & Same Day Sale	1,018	$71,260
		11/6/2001	Option Exercise & Same Day Sale	3,732	$227,167
				Paulter Total:	**$298,427**
Andrea Rabney	VP, Corporate Com. & IR	10/29/2001	Option Exercise & Same Day Sale	14,468	$1,012,760
		11/2/2001	Sale	11,253	$698,136
				Rabney Total:	**$1,710,896**
S. Joseph Tarnowski	Sr. VP, Manuf. Operations	10/29/2001	Option Exercise & Same Day Sale	9,324	$652,680
		11/2/2001	Sale	2,346	$145,546
				Tarnowski Total:	**$798,226**
Catherine Vaczy	VP, Legal & Associate Counsel	10/29/2001	Sale	2,466	$172,620
		10/29/2001	Option Exercise & Same Day Sale	6,430	$450,100
		12/6/2001	Sale	934	$67,192
				Vaczy Total:	**$689,912**
Larry Witte	VP, Research	10/29/2001	Option Exercise & Same Day Sale	17,147	**$1,200,290**
				Officer Total:	**$35,678,219**

* Estimated using closing share price on day of transaction, except for 10/29 sales (Tender Offer)

ImClone Employees' Stock Sales
12/1/2001 - 12/31/2001

Employee	Title	Date	Transaction Type	Shares	Price (Approx.)*
Henry Bon-Gil Koo	Research Associate	12/4/2001	Sale	148	$10,604
		12/4/2001	Option Exercise & Same Day Sale	375	$26,869
				Koo Total:	**$37,473**
Glen Noonan	Director, Quality Assurance	12/7/2001	Sale	2,300	**$162,035**
Hugh Dunne	Sr. Dir., Facilities & Security	12/13/2001	Sale	3,000	$208,830
		12/14/2001	Option Exercise & Same Day Sale	27,000	$1,890,000
				Dunne Total:	**$2,098,830**
Richard Thompson	Warehouse Manager	12/5/2001	Option Exercise & Same Day Sale	1,000	**$73,830**
Michael Barry	Director, Process Development	12/5/2001	Option Exercise & Same Day Sale	300	**$22,149**
Helen Kotanides	Senior Scientist I	12/5/2001	Option Exercise & Same Day Sale	1,000	**$73,830**
Ann Marie Choquette	Administrative Asst. II, Reg.	12/5/2001	Option Exercise & Same Day Sale	250	**$18,458**
Adelle R. Budd	Buyer I	12/5/2001	Option Exercise & Same Day Sale	500	**$36,915**
Erik Ramanathan	Director, Legal	12/5/2001	Option Exercise & Same Day Sale	1,156	**$85,347**
Jacqueline Doody	Scientist I	12/6/2001	Option Exercise & Same Day Sale	250	**$17,985**
Paul E. Windt	Manager, Clinical Trials	12/6/2001	Option Exercise & Same Day Sale	2,000	$143,880
		12/11/2001	Option Exercise & Same Day Sale	2,000	$140,780
				Windt Total:	**$284,660**
Rowland P. Spinks	MIS Associate	12/11/2001	Option Exercise & Same Day Sale	2,250	**$158,378**
Deborah Lynch	Director, Regulatory Affairs	12/11/2001	Option Exercise & Same Day Sale	2,500	**$175,975**
Delimir Branovich	Information Systems Technician	12/11/2001	Option Exercise & Same Day Sale	900	$63,351
		12/31/2001	Option Exercise & Same Day Sale	150	$6,969
				Branovich Total:	**$70,320**
Elizabeth C. Navarro	Research Scientist III	12/12/2001	Option Exercise & Same Day Sale	150	**$10,221**
Koons-Tomaszewski	Warehouse Supervisor	12/17/2001	Option Exercise & Same Day Sale	230	**$15,780**
Ivette Lugo	Buyer I	12/17/2001	Option Exercise & Same Day Sale	375	**$25,729**
John D. Watkins	Quality Contorl Scientist I	12/17/2001	Option Exercise & Same Day Sale	555	**$38,079**
Bridget Finnerty	Research Associate	12/19/2001	Option Exercise & Same Day Sale	200	**$12,320**
				Employee Total:	**$3,418,313**

* Estimated using closing share price on day of transaction, except for 10/29 sales (Tender Offer)

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DEVELOPED/OWNED/OPERATED BY DISTINGUISHED HOTELS AND RESORTS

9700 BAY STREET MIAMI, FLORIDA 33141

April 4, 1991

Mr. John Landes
ImClone Systems Incorporated
180 Varick Street
New York, New York 10014

Dear John:

Pursuant to Sherwood M. Weiser's demand for inspection and our conversation this morning, enclosed are copies of the following documents:

1. The June 24, 1986, letter from Sherwood M. Weiser to Dr. Samuel D. Waksal.

2. The July 11, 1986, letter from Samuel D. Waksal, Chief Executive Officer of ImClone Systems Incorporated, to Sherwood M. Weiser.

3. Stock Certificate #36 of ImClone Systems Incorporated certifying that Sherwood M. Weiser Trustee is the owner of 12,000 shares.

Please send via Federal Express all the information requested by Mr. Weiser, as well as all other materials given to shareholders since the audited financial statements through March 31, 1988. Per our conversation, this information should be sent via Federal Express for our receipt by Monday, April 8, 1991.

Thank you for your attention to this matter.

Sincerely,

Steven J. Horton
Vice President
Finance and Development

SJH:gb
cc: Sherwood M. Weiser

via fax to 212/645-2054

TCC is a joint venture of The Continental Companies and Tobishima Associates, Ltd.

HCEC 36512
Confidential Treatment Requested by ImClone Systems, Inc.

IMCL DOJ 0049032

CONFIDENTIAL

The Continental Companies

Development Counsel Corporation
of Distinguished Companies

3250 Mary Street
Miami, Florida 33133
Telephone (305) 443-3693

June 24, 1986

VIA: FEDERAL EXPRESS

Dr. Samuel D. Waksal
ImClone Systems Inc.
180 Varick Street
New York, N. Y. 10014

Dear Sam:

Enclosed please find my check in the sum of $90,000 made out to Biotechnology Holding Company, which is the full payment for 12,000 shares at $7.50 per share of ImClone Systems Inc. I would appreciate it greatly if you would put the shares in my name as Trustee, since I may want to give away some of them. I am also enclosing the information on the cruise for the National Foundation for Advancement in the Arts which gives the details of the trip, which begins on July 4 until July 6.

Please let my secretary, Gwen Newell, know when you plan to arrive and we will make sure that you are picked up at the airport.

Judy and I are looking forward to seeing you and your daughter and expect that it will be a fun couple of days. My sincerest thanks for inviting me into ImClone. I am certain that it will be a great success with your leadership.

My kindest personal regards.

Cordially,

Sherwood M. Weiser, Chairman

smw:gn
enclosure

CONFIDENTIAL

ImClone Systems Incorporated
180 Varick Street New York, NY 10014

July 11, 1986

Mr. Sherwood M. Weiser
Chairman & CEO
The Continental Companies
3250 Mary Street
Miami, Florida 33133

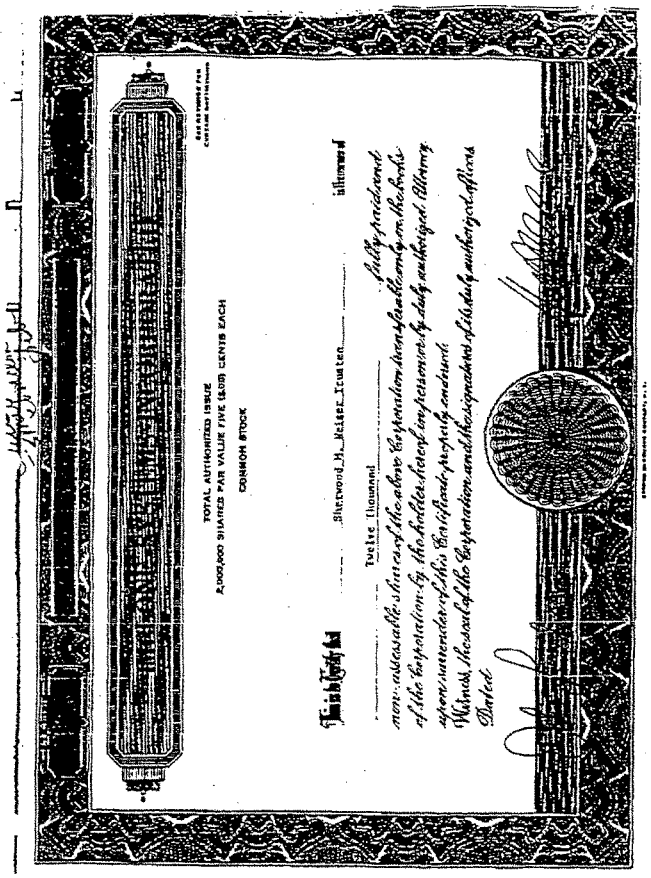
Dear Mr. Weiser:

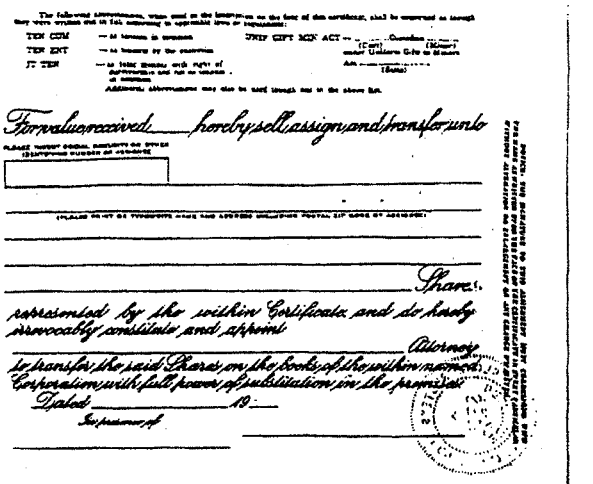
We are in receipt of your check to Biotechnology Holding Company for $90,000. We will transfer 12,000 shares of ImClone Systems Inc. common stock to you as trustee. The certificate will be in the name of Sherwood M. Weiser trustee. Please let us know if this is acceptable. We look forward to having you as a part of our extended corporate family.

Sincerely,

Samuel D. Waksal
Chief Executive Officer

SW:mm





For value received, hereby sell, assign and transfer unto

Shares

represented by the within Certificate, and do hereby irrevocably constitute and appoint

Attorney

to transfer the said Shares on the books of the within named Corporation with full power of substitution in the premises.

Dated _____ 19__

In presence of

_____ _____

HCEC 36516
Confidential Treatment
Requested by ImClone
Systems, Inc.

IMCL DOJ 0049036

CONFIDENTIAL

ImClone System Incorporated
180 Varick Street, New York, N.Y., 10014
(212) 645-1405

April 4, 1991

Mr. Steve Horton
TCC
3250 Merry Street
Miami, FL 33133

Dear Steve:

Per our conversation today, I am sending down copies of ImClone's audited financial reports dated March 1989 and March 1990, as well as letters to Shareholders that have gone out in that period since March 1988.

Please contact me with any questions that you have about the Company.

Very truly yours,

John B. Landes
Vice President
Legal & Administration

JBL/ia

TCC

DEVELOPERS OWNERS OPERATORS
OF DISTINGUISHED HOTELS AND RESORTS

[illegible] STREET
MIAMI FLORIDA [illegible]

TELEPHONE [illegible]
TELEFAX [illegible]

SHERWOOD M. WEISER
CHAIRMAN & CHIEF EXECUTIVE OFFICER

April 11, 1991

Mr. John B. Landes
Vice President
Legal and Administration
ImClone Systems Incorporated
180 Varick Street
New York, New York 10014

Dear John:

I received Steven J. Horton's letter to you dated April 4, 1991, and your responding letter of the same date with the following attachments: audited financial statements of ImClone Systems Incorporated ("ImClone") through March 31, 1988, March 31, 1989 and March 31, 1990 and Letters to Shareholders dated November 21, 1988, November 15, 1989 and January 17, 1991. I have the following questions which I request that you immediately respond to:

1. As I have been a registered shareholder of ImClone since 1986, why was I not on the shareholder list?

2. Since October 1988 when I received the financial statements covering the period from April 26, 1984 to March 31, 1988, I have not received any financial reports. Why didn't I receive any information? Why didn't ImClone respond to my prior requests?

3. When and where was the last shareholders' meeting? Please send me any materials given to the shareholders and any notes and/or results of the meeting.

4. When and where will the next shareholders' meeting be?

5. I am very interested in determining the compensation from ImClone to ImClone's officers and directors. I am also interested in the stock warrants and options programs since the March 31, 1990, audited financial statements state there are 863,000 warrants exercisable at $6.00 per share and approximately $400,000 options exercisable, much of them at $.05-$6.00 per share.

TCC IS A JOINT VENTURE OF THE CONTINENTAL COMPANIES AND TOBISHIMA ASSOCIATES, LTD

Thus, for each officer and director at March 31, 1990 and as of March 31, 1991, I request the following information for each of the prior three years:

a. wages received or accrued
b. information regarding employment contracts, including but not limited to guarantees, term of agreement, wage scale, termination clauses, etc.
c. dividends received or accrued
d. fees received or accrued
e. information regarding consulting agreements, or other types of agreements
f. details of all stock warrants granted, exercised and exercisable, including dates, prices per share, expiration periods, etc.
g. details of all stock options granted, exercised and exercisable, including dates, prices per share, expiration periods, etc.
h. number of shares purchased and sold by the officer/director directly or by their families or entities under their control
i. any guarantees to them or by them
j. other benefits provided, including but not limited to pension plans, health insurance, automobiles, etc.
k. any other pertinent information

Your rapid response to my questions will be most appreciated.

Cordially,

Sherwood M. Weiser

SMW:gb

ImClone Systems Incorporated

MEMORANDUM

April 23, 1991

To: File
From: JL

Re: Corporate/Shareholders

Spoke with Sherwood Weiser in connection with his letter to us of April 11, and indicated that we would send down to him a Stock Certificate to replace that which he has, and also a Stock Purchase Agreement for him to sign so that everything can be appropriately in place as of June 1986.

He was looking to find out about the current status of the Company, and I filled him in. He seemed satisfied with this.

In terms of what he wants from his April 11 letter, if he has information about the transactions with the officers, and that he feels that all things are being done correctly, then he will be more than satisfied.

corp/m10423.sh

ImClone Systems Incorporated
180 Varick Street, New York, N.Y. 10014
(212) 645-1405

April 23, 1991

Mr. Sherwood M. Weiser
TCC
3250 Mary Street
Miami, FL 33133

Dear Mr. Weiser:

I very much appreciate the opportunity that we had yesterday to discuss ImClone and its current status. Please feel free to contact me at any time with questions that you might have about the Company.

Our most recent Shareholder meeting was held February 8, 1991, and covered the activities of the prior fiscal year. This meeting had been delayed due to the pendency through the Fall of a significant agreement with our newest strategic pharmaceutical partner, the German company E. Merck. That Agreement was completed in mid-December 1990, and funds the Company in its efforts toward a melanoma vaccine over a period of three years in the amount of roughly $14 million total.

Once the Agreement was in place, we scheduled the Shareholder meeting. Business of the meeting was the re-election of previous years' Directors. Dr. Sam Waksal gave a presentation on the current status of ImClone and its scientific projects. We made financials through 12/31/90 available in the Shareholder Notice package, which I believe I had sent down to Steve Horton. In case I did not, I am sending another.

We intend to hold our next Shareholder meeting sometime in the early Fall, most likely September, as the audit report on our 3/31/91 fiscal year should be completed in mid-Summer. You will receive all future mailings.

In reference to your question of stock compensation to the Directors, I call your attention to the discussion of the Warrants in the footnotes of the audited financial reports that you have. A total of 750,000 Warrants to purchase common stock at an exercise price of $6.00 went to Sam Waksal and Harlan Waksal in the Spring of 1987. These were approved by the full Board in recognition of their significant contributions to the Company. Other than that, the Waksals have a small number of non-qualified options, and their salaries are significantly below industry scale.

In connection with your stock, as we have discussed, I would like to replace the certificate you hold with one showing the proper June 1986 date, so that the records of the Company can be completely accurate. Also, so that these records can be complete, we should have on file a Stock Purchase Agreement, effective June 1986, between yourself and Sam Waksal, and I have enclosed two copies, signed by Sam, for your signature. Please sign them and return one to me. In the meantime, I shall prepare the replacement certificate to exchange for that which you hold.

Please contact me with any questions.

Very truly yours,

John B. Landes
Vice President
Legal & Administration

JBL/ia
cc:Dr. Samuel D. Waksal

In connection with your stock, as we have discussed, I would like to replace the certificate you hold with one showing the proper June 1986 date, so that the records of the Company can be completely accurate. Also, so that these records can be complete, we should have on file a Stock Purchase Agreement, effective June 1986, between yourself and Sam Waksal, and I have enclosed two copies, signed by Sam, for your signature. Please sign them and return one to me. In the meantime, I shall prepare the replacement certificate to exchange for that which you hold.

Please contact me with any questions.

Very truly yours,

John B. Landes
Vice President
Legal & Administration

JBL/ia
cc:Dr. Samuel D. Waksal

AFFIDAVIT OF SAMUEL D. WAKSAL

I, Samuel D. Waksal, being duly sworn, depose and say:

1. I am President and Chief Executive Officer of ImClone Systems Incorporated.

2. I reside at 150 Thompson Street, New York, New York, 10012.

3. On or about June 24, 1986, 12,000 shares of ImClone common stock were intended to be transferred by myself to Sherwood M. Weiser, Trustee, and I received full compensation in the amount of $90,000 for the transfer of such stock.

4. The stock was mistakenly purported to be transferred from Biotechnology Holdings Company to Mr. Weiser as Trustee. Biotechnology Holdings Company is a company established by myself, and Biotechnology Holdings Company did not and has not held ImClone Systems common stock. Said stock purported to have been transferred from Biotechnology Holdings Company should be considered to have been transferred by myself, including the stock referenced in the above transaction.

Samuel D. Waksal

Sworn to before me this ____ day of _____, 1991

Notary Public

HCEC 36624
Confidential Treatment Requested by ImClone Systems, Inc.

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Barron's

Monday, June 28, 1993

Outside the Lab

Biotech CEO's Lifestyle Raises Investor Eyebrows

By Edward A. Wyatt

SAM Waksal wants to set the record straight: "If I'm being viewed as someone who's hanging out with movie stars, that's a view that's not correct."

It's an unusual denial for an immunobiologist to have to make. But Waksal, president and chief executive of ImClone Systems, a New York-based biotechnology company, is far from your average gene cloner.

He has co-produced two feature films. His office boasts snapshots of him with Sean Connery and Dustin Hoffman, as well as a photo of the unlikely quartet of Waksal, actress Virginia Madsen and Mikhail and Raisa Gorbachev. ("Virginia was my date," Waksal confides.) A recent profile in Avenue, a New York City monthly chronicling life among the silk-stocking set, shows him in a "typical day" lunching with actor Matthew Modine. The two are dining at Sam's, one of two restaurants Waksal co-owns with movie producer Stephen Crisman, husband of actress Mariel Hemingway. Twice already this year, Waksal has popped up in the gossip columns of Vanity Fair magazine.

Yet Waksal bristles at the notion that he spends more time with the jet set than a chemistry set. "I'm not having dinner with Barbra Streisand every week. It's a rare event for me to hang out with a movie star. It's a rare event. I just don't do it."

The fortunes of ImClone Systems might not rise and fall on the strength of Waksal's social calendar. But the conspicuous profile cut by the 45-year-old scientist has raised eyebrows and hackles among a number of ImClone investors.

Controversy, it seems, has long pursued Waksal, following him to ImClone from the academic community, where he left behind a number of soured relationships with fellow researchers. Once at ImClone, industry observers say Waksal's propensity to pursue the current "hot topic" in the still-young field of biotechnology left the company adrift. But though eclecticism can be valuable, even desirable, in academia, it's not so highly esteemed in a publicly held company. What emerges from interviews with friends, former colleagues, business associates and Waksal himself is a portrait of egoism that, left unchecked, could take a toll on the public's investment in ImClone.

Waksal readily admits he can cause a stir: "I'm a controversial character, because I'm a character." But he maintains that his extracurricular activities -- the films, the restaurants, the celebrity benefits -- don't detract from his work at ImClone. "The thing I'm committed to most is building a great company that does important things. That's my job. I have a lot of hobbies, but my job is managing the science, and I'm doing it incredibly well. Those people that say, 'He's running around with movie stars, he should be managing the science,' don't sit here and watch things get done."

Indeed, Waksal has many supporters -- at the company, in academia

and in industry. He points out that ImClone has recruited a number of top researchers to its board and its labs, among them Vincent T. DeVita Jr., former director of the National Cancer Institute, and Arnold Levine, a world-renowned biologist at Princeton.

"I think Sam is a very good CEO," says Robert Goldhammer, chairman of ImClone's board of directors. "He's a remarkable fellow in many ways. He understands the science extremely well. And he understands the biotechnology industry. I'd certainly rather have him than not have him."

And ImClone undoubtedly has made progress since its founding in 1984. The company is awaiting the okay from the Food and Drug Administration to expand its Phase I trials of its lead product, a potential cancer vaccine, to three clinical sites. The vaccine, ImClone believes, might prevent recurrence of cancer in patients already treated for initial outbreaks of melanoma or small-cell lung cancer.

In addition, ImClone has sold licenses for several products to such formidable allies as American Cyanamid, Abbott Laboratories and Japan's Chugai Pharmaceutical. The deals demonstrate some of Waksal's obvious strengths: He's a good salesman, a charmer who can convince potential partners of the value of ImClone's science.

Waksal also can be an astute businessman. While other biotech companies prefer suburban office parks in California or Massachusetts, Waksal set up his microscopes in a converted shoe factory in a grimy industrial section of lower Manhattan. That allowed the company to use low-cost industrial-development revenue bonds to renovate the facility. And while others in the industry have been reluctant recently to test the market to sell shares, ImClone last month raised $10 million in its first stock offering since going public in November 1991.

The offering secured ImClone's cash needs through 1994; by then it expects royalty revenues to flow from licensing deals. But ImClone will likely need loads more cash to propel its cancer vaccine through clinical trials.

While ImClone's most advanced scientific programs target cancer, that wasn't always so. In fact, critics cite Waksal's lack of focus as the company's most persistent problem. In its short history, ImClone has pursued such diverse product areas as molecular modeling, vaccines for sexually transmitted diseases and diagnostics. Scientists managing those programs came and went.

Former employees say the constant changes, combined with Waksal's short fuse, created a chaotic atmosphere in the young company's labs, with researchers being pulled haphazardly from one project to another. Waksal, a slight, balding man of gaunt frame whose most imposing features are his intellect and ego, sees it as simply his way of producing results: "I'm one of the few CEOs, I think, in this industry who can walk back to the labs and say 'Show me your data,' and say 'Why didn't you do this control' and 'Why didn't you do that control,' and I do it."

Yet Waksal feels stung by the charge he lacks focus. "Obviously, this is something I'm sensitive to," Waksal says. "I know the criticism. I get it internally and externally. I hope that success will allow people to come back to me and say, 'You

were right.' If
I'm wrong -- I don't think I'm going to be wrong."

Any result will likely be long in coming. "In cancer clinical
trials, it's often difficult to prove anything," says one
institutional investor who specializes in biotechnology and who owns
ImClone stock. "I think ImClone does some good science, but I don't
think anyone would argue it's the best science in the world. And
they've always been in that two-year window of cash. These stocks
don't go anywhere with less than two years of cash on the balance
sheet."

By that measure, the verdict is rather clear. After going public
at $14, ImClone's stock hit $27 early last year before the group
fell out of favor, and the shares now linger at one-quarter their
all-time high. At that level, it's no surprise ImClone's May
offering was oversubscribed: The $7 price was below the $8.88 a
share paid by several venture-capital investors before the IPO.

For a company where cash is obviously a crucial concern, ImClone
has been doing some curious things. In the March 1991 fiscal year,
ImClone loaned Waksal $70,000 and gave him "miscellaneous cash
advances" of $88,438. The loan and advances were repaid with
interest, but the following year ImClone made another $117,000 in
noninterest-bearing cash advances to Waksal. And in the nine months
ending Dec. 31, 1992, the company loaned its CEO another $275,000.
(He has since consolidated the outstanding loan and unpaid cash
advances into a single $374,000 note, maturing at year-end and
bearing 10% annual interest.)

The loans from ImClone came as Waksal earned salary and cash
bonuses of $981,250 over the 33-month period, putting him among the
best-paid biotech CEOs. Meanwhile, Waksal was raising cash in other
ways: In July 1992, he sold 33,000 shares of ImClone stock in the
open market for $289,260. And from December 1992 through January
1993, Waksal cashed in $448,850 worth of stock of Medicus
Pharmaceutical, from whose board of directors he had recently
resigned.

Where has all that cash been going? "The loan that's out there
right now is for renovating my loft," Waksal replies, referring to a
7,000-square-foot apartment he's constructing in Soho, the
fashionable downtown art district, about a half-mile from ImClone
headquarters. Waksal also has put together an impressive collection
of modern art and ancient relics certain to be prominently featured
in the new abode.

Public companies commonly make loans to officers to buy new
houses or relocate, and Waksal contends his borrowings have drawn
undue concern. Goldhammer, ImClone's chairman, shrugs off a question
about the loans -- but at the same time discloses that ImClone now
has a new, no-loan policy: "The money is being paid back. It will
not be loaned to him again. So it's a historical event rather than
an ongoing one."

But shareholders who have funded Imclone's $53 million
accumulated deficit deserve to know where their money is going.
Waksal concedes he didn't have the money for his apartment because
he had loaned a big chunk of cash to Sam's Restaurant. (The
brasserie's moniker comes from Mariel Hemingway's nickname.) In
March, the parent of the chic Manhattan eatery filed for Chapter 11

bankruptcy protection. Its biggest creditor: Sam Waksal, who owns a 23.4% stake and is owed $722,499.

The restaurant loans, Waksal explains, were "a real error. I put a little money in -- it wasn't a lot initially, but as the years went by they came to me to pay shortfalls and pay shortfalls and pay shortfalls. I suddenly got into a position where the corporation I invested in owes me all this money." But, he says adamantly, "No money from ImClone ever went to a restaurant."

Waksal professes that he's learned a hard lesson: "Stay in areas that you understand. Medical companies are things I understand quite well. I'm obviously a real bad judge of investing in the food business. More importantly, nobody should invest in restaurants. They are notorious disasters."

That said, Waksal has invested in a new restaurant. Alexis Stewart, Waksal's former girlfriend of four years and the 24-year-old daughter of homemaker extraordinaire Martha Stewart, is trying to open an upscale diner in Southampton, Long Island. Objections from the tony hamlet's planning board, however, have so far thwarted the effort. The stainless-steel diner sits unused on property bought for $200,000 in February 1992 by Uncle Vanya Enterprises, which according to Suffolk County tax records has the same address as ImClone Systems.

"I did put some money in," Waksal admits, but only because the Stewarts are personal friends. "But it's not my restaurant. I made a little investment so that I own a piece of the property and that's it. I have no involvement. . . . A couple of years ago I stopped putting money into anything I didn't feel I had total control over."

Even Waksal's friends assert that it's simply the man's largesse that causes him problems. Charles Antell, a venture capitalist who owns more than 100,000 ImClone shares and who describes himself as close to Waksal and the company, observes: "Sam is too nice a guy sometimes. He's tried to be helpful to people. He made some loans and people took advantage of him."

Antell must know how it feels. He sued Waksal in February because Waksal hadn't repaid $100,000 he borrowed from Antell a year earlier. "That had nothing to do with the company," Antell maintains. "It was personal between me and Sam Waksal. Unfortunately, I felt I had to file suit to get my money back."

(See related letter: "Letter to the Editor: National Enquirer II?" Barron's -- July 26, 1993.)

Antell hasn't been Waksal's only dissatisfied creditor. There's the IRS and New York State Tax Commission, which filed liens for $13,878 and $5,667, respectively, last year. A private test-preparation service in New York filed a breach-of-contract suit for $14,830 in January, asserting that Waksal didn't pay for a daughter's SAT prep course. (Waksal has two college-age daughters by a previous marriage.) A former landlord, a realty agency, an investment partnership, even a contractor on Waksal's new apartment -- all have sued Waksal over allegedly unpaid bills.

Waksal is stalwart in his defense. The tax bills, he maintains, have been paid, as has the testing-service bill. The partnership dispute was settled. Other disputes were dismissed or settled or are on their way to being so. Waksal volunteers that he countersued the

apartment contractor, which he says he fired when his roof caved in.
"Every lawsuit I've ever been involved in isn't for the reason you
think it is," Waksal explains. "I'm a bit litigious at times. I'm
willing to do things that I probably shouldn't do, but it's not for
the reasons you think. The lawsuits aren't because people aren't
getting paid."

If Waksal's only sin is poor management of personal finances, he
can hardly be condemned. Entrepreneurs often have difficulty making
the transition to public fiduciary. But other issues have long
dogged Waksal and, by association, ImClone. Among them is a trail of
sometimes vicious accusations by former colleagues in scientific and
academic fields. While stories alleging scientific and financial
chicanery could be dismissed as jealousies over Waksal's
private-sector success, effects of the widespread rumors linger:
Three prominent institutional investment firms or advisers
interviewed by Barron's cited the stories as a reason they shied
away from ImClone.

As it turns out, Waksal is aware of many of the stories, and he
seems eager to clear the air. "I know there are all sorts of rumors
out there about tons of things, and they get so varied and so
ridiculous they've become absurd," he says.

Waksal has a distinguished scientific resume: After earning a
Ph.D. in immunobiology from Ohio State in 1974, he worked briefly at
Stanford and joined the National Cancer Institute in 1975. From 1977
to 1982, Waksal was a senior scientist at the Tufts University
Cancer Research Center; he then served as director of
immunopathology at the Mount Sinai School of Medicine from 1982 to
1985.

Those appointments were not wholly without conflict. Two former
colleagues at Mount Sinai say Waksal departed under a cloud of
dispute over his division's financial condition and ownership of
some molecular modeling technology that ImClone later pursued.

"There was no dispute with the administration when I left Mount
Sinai," Waksal responds. "There were scientists who were involved
with us early on at Mount Sinai that were working in the molecular
modeling field, and there was a dispute, with ImClone. That dispute
ended."

What remains, however, are many hard feelings he engendered at
Mount Sinai, even though ImClone retains some collaborations with
the school: "There were people at Mount Sinai that I had some big
fights with," Waksal recalls. "There are people there who hate me.
I, at times, am arrogant and abrasive. People either hate me or like
me. I'm not someone who no one knows is there. They know I'm there."

It was after some of those fights that Waksal took a leave of
absence from Mount Sinai and founded ImClone with his younger
brother, Harlan Waksal, an M.D. who now is the company's chief
operating officer and a director. Sam Waksal later decided not to
return to Mount Sinai, although he denies persistent rumors that he
was fired or forced to resign. Mount Sinai officials declined to
comment. Sam and Harlan are ImClone's largest shareholders, with 13%
and 10%, respectively, of ImClone's 9.3 million shares outstanding.

A more perplexing rumor overshadows Waksal's legacy at Tufts:
Several former colleagues tell the story that while he

was there,
Waksal once made medical rounds at New England Medical Center
impersonating his doctor-in-training brother Harlan, who at the time
was a Tufts medical student.

Sam Waksal is obviously familiar with the story, and offers this
explanation: "There was a patient of Harlan's who was a very nice
lady who spoke only Yiddish. And Harlan, when he wasn't in town at
one point, wanted me to go talk to her because she loved him. So I
went and talked to her. That was the scope of it. I didn't make
rounds for Harlan. It's so silly it's not to be dignified with
discussion. I haven't heard about that for a long time."

The reason the story continues to surface, a dozen years after
the fact, stems from the likely cause of Harlan's absence around
that time. On Feb. 14, 1981, Harlan Waksal, then 28, was arrested in
the Fort Lauderdale International Airport. Two undercover police
officers stopped Harlan after determining he fit a "drug courier
profile." During a search, the officers found more than two pounds
of cocaine in Harlan's carry-on bag and in his underwear.

On April 27, 1982, in a nonjury trial in federal court in Miami,
Harlan Waksal was found guilty of possession of cocaine with intent
to distribute and was sentenced to nine years in prison and a
five-year special parole term. He appealed, and on July 11, 1983,
the U.S. Court of Appeals for the 11th Circuit overturned the
conviction, ruling that "the search resulted from an illegal seizure
without a valid consent." The ruling threw out the evidence; the
case wasn't retried, and Harlan served no time.

Therefore, SEC regulations didn't require disclosure of the
incident when ImClone went public. Some institutional investors and
brokerage firms were aware of it; two specifically cite it as a
reason they haven't invested in ImClone.

Both Sam and Harlan Waksal speak forthrightly of the affair. "It
was a dramatic mistake in judgment," says Harlan. "I did it as a
favor for someone, and it's a favor I have obviously regretted." He
maintains he was neither using drugs at the time nor has he used
them since, and he says it was the only time he ever tried to
transport drugs.

Sam Waksal echoes his brother: "It was something that happened
once in Harlan's life when he was very young, and it has nothing to
do with this company." Regarding disclosure of the issue, Sam
replies: "All the bankers, the lawyers, the board always knew about
it. But if we ran around talking about it, it would be very hurtful
to somebody. It hurts me that he has to continue hearing about it 12
years later.

"Harlan is one of the brightest people I know. He's a genius.
Every director that knows Harlan will tell you what a great person
he is. And every shareholder that knows Harlan probably sometimes
would prefer that he had a higher position in this company, because
there would never be a question about focus with Harlan."

Indeed, people who have worked closely with ImClone profess that
it is Harlan who keeps Sam in check. While Sam is good at
embellishing a story, says one person familiar with the company,
"I've found what Harlan tells me will check out 100% of the time."

And while Harlan's presence at ImClone raises

concerns about
nepotism, Sam stresses that "Harlan is not here because he's my
brother; he's here because of how good he is."

Still, Sam Waksal is the guiding force behind ImClone Systems,
and therefore the company's move toward commercialization depends
primarily on his ability to subdue his more irascible instincts.

Waksal firmly believes that he can both pursue good science and
maintain his other interests. "I think I've built a company that has
tremendous potential and that's going to be successful. And I don't
say that glibly. I say that because I understand this company and
this industry." While obviously some institutions and persons don't
like Waksal or ImClone, others do, and he makes no apologies for
either his lifestyle or his zeal.

"People think I'm too this or too that, or I'm too controversial.
That as CEO of ImClone I should be very, very quiet, I should do
nothing else but run this company, and that's it. That's not me.
It's just not me. And it's not gonna be me."

---- INDEX REFERENCES ----

COMPANY (TICKER): IMCLONE SYSTEMS INC. (IMCL)

MARKET SECTOR: CONSUMER CYCLICAL; TECHNOLOGY (CYC TEC)

INDUSTRY: BIOTECHNOLOGY; ALL ENTERTAINMENT & LEISURE; MEDICAL & BIOLOGICAL TECHNOLOGY; RESTAURANTS (BTC ENT MTC RES)

NEWS SUBJECT: BIOGRAPHY; MANAGEMENT ISSUES; CORPORATE PROFILES (BIO MNT PRO)

REGION: NORTH AMERICA; NEW YORK; UNITED STATES (NME NY US)

Word Count: 3296

6/28/93 BARRONS 14

END OF DOCUMENT

4

ImClone Systems Incorporated
Interoffice Memorandum

Memorandum

DATE:	*January 23, 1998*
TO:	*Robert F. Goldhammer, Harlan W. Waksal, Samuel D. Waksal*
FROM:	*John B. Landes*
SUBJECT:	*Executive Committee of the Board of Directors*

This will serve as minutes to be kept with the minute books of the Executive Committee of the Board of Directors with respect to the actions set forth in this memorandum. Attached hereto is a promissory note dated January 22, 1998, signed by Samuel D. Waksal, pursuant to the exercise of Warrant No. RW0018 for the exercise of 87,305 ImClone shares.

Pursuant to the terms of the Warrant, a promissory note to the Company has been signed by Dr. Waksal in the amount of $130,957.50 (number of shares X the exercise price of $1.50). Both Dr. Harlan Waksal and Robert F. Goldhammer, members of the Executive Committee, have approved such note, acknowledging the intent stated in the note that it be repaid within 90 days hereof. The note states further that any right to extend such maturity date beyond 90 days from January 22, 1998 (April 22, 1998) would require a vote of the full Board of Directors.

cc: Catherine M. Vaczy

lz/3577

SECURED PROMISSORY NOTE

Date: January 22, 1998
New York, New York

FOR THE VALUE RECEIVED, the undersigned, Samuel D. Waksal, residing at 150 Thompson Street, New York, New York, hereby promises to pay to the order of ImClone Systems Incorporated, 180 Varick Street, New York, New York, 10014, on or before the second anniversary of the date hereof the principal sum of **$130,957.50**, and to pay interest on the unpaid principal sum on the first anniversary of the date hereof and on the stated maturity or any accelerated maturity hereof at the rate per annum equal to the prime or base rate announced by Chemical Bank, N.A., at its office in New York, New York on the date hereof, but not less than the Federal short-term rate, as defined in Section 1274(d) of the Internal Revenue Code of 1986, as amended.

It is the interest of the undersigned to pay the principal within ninety (90) days. Right to extend the maturity beyond that date will require the approval of the full ImClone Board of Directors.

This Note is given in connection with the exercise of a certain Warrant, dated 5/6/91, to purchase shares of common stock of ImClone Systems Incorporated. This Note is secured by a pledge of the shares of common stock purchased upon exercise of such Warrant, or by the collateral described in Attachment A, as required by the Company.

In the event that:

(i) the undersigned shall fail to pay any installment of interest within ten (10) business days after such installment is due; or

(ii) the undersigned shall become insolvent, have any action commenced against it under any bankruptcy, insolvency or similar statute, or take any action for relief under any bankruptcy, insolvency or similar statute;

then the holder of this Note, by notice to the undersigned, shall be entitled to declare the entire unpaid balance of this Note (together with interest accrued thereon) to be immediately due and payable in full, except that no such notice or declaration shall be required if an event described in clause (ii) above shall have occurred, in which case the entire unpaid balance of this Note, together with interest accrued thereon, shall be immediately due and payable.

Presentment for payment, notice of dishonor, protest and notice of protest are hereby expressly waived.

The undersigned may prepay this Note in whole or in part at any time and from time to time.

This Note is executed under, and is to be construed in accordance with the laws of, the State of New York.

IN WITNESS WHEREOF, the undersigned has duly executed this Note as of the day and year first above stated.

Samuel D. Waksal

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ImClone Systems Incorporated

Minutes of the Audit Committee Meeting Held on February 12, 1998

Pursuant to notice duly given a meeting of the Audit Committee of the Board of Directors was held on February 12, 1998 at the Offices of Concord International, 667 Madison Avenue, New York, NY commencing at 10:00 a.m. Present were all the members of the Committee (Messrs. Barth, Kies, Kopperl and Miller) together with Robert F. Goldhammer, Chairman of the Board, Harlan W. Waksal, Executive Vice President and Chief Operating Officer, and Carl S. Goldfischer, Vice President, Finance and Chief Financial Officer. The purpose of the meeting is described in the attached memorandum dated January 30, 1998 (excluding enclosures) from the Chairman of the Committee to the attendees.

After thorough discussion the Committee, Mr. Goldhammer and Dr. Waksal agreed that the following policies, procedures and suggestions would be communicated by Messrs. Goldhammer and Kopperl to Dr. Samuel D. Waksal, President and Chief Executive Officer, in a face-to-face meeting at the earliest practicable opportunity.

1. Political Contributions. Regardless of the proposed amount or recipient, each prospective political contribution must be approved in advance by the Chairman of the Board of Directors.

2. Charitable Contributions. The Corporation already has a well articulated policy and annual budget which are to be followed faithfully. The 1998 budget limit is approximately $50,000, the Committee was informed. Contributions, each of which must receive appropriate corporate approval in advance, are to be made to tax exempt medical and/or New York oriented charitable organizations only.

3. Updating Corporate Policy Regarding Travel & Entertainment Expenditures By Senior Managers. At an early date such a policy statement applicable to Corporate Vice Presidents and higher ranking officers will be prepared by the financial or legal staff for review by senior management, KPMG Peat Marwick and the Committee. Upon approval, the statement will be transmitted to all appropriate individuals.

4. Annual Budgets. Prior to the beginning of each year and periodically during the year, the Committee will review the travel and entertainment budgets of the CEO individually and of the CEO and his direct reports. The budgets and expense reports of the CEO individually should show the following information for each of the indicated categories:

   Purposes

   (1) Attending medical conferences and meetings with government
   (2) Pursuit of corporate alliances, licenses, other strategic initiatives

(3) Personnel matters
(4) Meetings with investors (existing or potential), security analysts, portfolio managers and bankers
(5) Meetings about scientific research, product trials or other commercial activities

Expenditures for Each Such Purpose

Expenditures are to be budgeted and reported for each of the foregoing purposes by the following line item classifications:

(1) Airfare
(2) Other travel
(3) Lodging
(4) Travel meals
(5) Entertainment of investors, security analysts, portfolio managers and bankers
(6) Entertainment of scientists
(7) Entertainment for other corporate purposes

5. Documentation. None of the CEO's business expenditures will be reimbursed until proper and complete documentation has been received in a timely fashion by the COO or the CFO whose approval is required.

6. Suggestions. The Committee believes that common sense and good judgment should be used regarding individual and aggregate expenditures for:

Meals and wine. Specifically as to wine, the maximum should be $50-100 per bottle.

Travel Mode. Existing ImClone travel policies should be followed faithfully. These preclude reimbursement of premium fares except in long distance trips or critical situations.

Tickets to Sporting and Other Events. The cost of tickets to sporting and other events can be prohibitive, particularly if not obtained well in advance. Such purchases should not be made, barring exceptional circumstances.

Lodging. Clearly "Motel 6" is neither necessary nor appropriate. However, five star European hotels such as the Crillon and occupying a suite are inappropriate unless a significant discount can be obtained or, in the case of a suite, its use will include conducting one or more business related meetings with several attendees.

After reviewing these policies, procedures and suggestions, the Committee instructed Messrs. Goldhammer and Kopperl to prepare a summary of them to be presented to and discussed with the CEO at the earliest practicable opportunity. Thereupon, after a motion to adjourn was duly made, seconded and unanimously voted, the meeting was adjourned at 11:40 a.m.

Addendum

From 4:10 p.m. until 5:45 p.m. on Thursday, February 12, 1998, Messrs. Goldhammer and Kopperl met with Dr. Samuel D. Waksal in Mr. Goldhammer's office at 667 Madison Avenue, New York City to carry out the foregoing instructions of the Committee. Dr. Waksal acknowledged that he understood and will comply with the Committee's requirements and proposals regarding expenditures by the CEO.

The Chairman of the Board or the Chairman of the Audit Committee will deliver a copy of the minutes of the February 12th Audit Committee meeting to the CEO as well as the COO, CFO and members of the Committee.

Robert F. Goldhammer, Chairman of the Board

Paul B. Kopperl

Paul B. Kopperl, Chairman of the Audit Committee

bd/audit/298orig.doc

Memorandum

To: Messrs. Richard Barth, Carl Goldfischer, Robert Goldhammer, David Kies, William Miller, Harlan Waksal

From: Paul Kopperl

Date: January 30, 1998

Re: ImClone Systems Inc. -- February 12th Meeting To Discuss CEO's Expenses

This will confirm our 10:00 o'clock meeting on Thursday morning, February 12, 1998 at Bob Goldhammer's office at Concord International, 17th Floor, 667 Madison Avenue at 61st Street, New York City. Bob's phone and fax numbers are (212) 759-5013 and (212) 759-1503 respectively.

The purposes of the meeting are for the Audit Committee together with Messrs. Goldhammer, Waksal and Goldfischer (1) to review Sam Waksal's expenses for which he has claimed reimbursement as to the relevance of their stated business purpose, amount and adequacy of documentation, (2) to establish rules for the future which can in fact be implemented and will be effective and (3) to inquire whether there have been material charitable or political contributions by the Company which are for all intents and purposes T&E expenditures.

One issue which I ask the meeting to address is whether, at this stage of ImClone's development, the CEO needs to spend such a considerable amount of his time and the Company's money on investor relations when we employ both a CFO and a Director of Investor Relations.

It is possible, I have heard, that Sam may wish to attend the meeting. That's OK with me, provided he will allow us 30-40 minutes at the outset to discuss our varying opinions in private. I would also like to state the obvious: this is not a witch hunt. Rather I have requested the meeting to deal with the need to establish effective reporting of and control over the CEO's expenditures. As it is now, too many of us are required to commit an increasing amount of time to a process which, in my opinion, provides inadequate documentation and ineffective results.

To facilitate your preparation for this meeting I am enclosing summary expense statements covering the period from 12/1/95 through 8/31/97; the 1/16/98 memo from ImClone's Controller, Paul Goldstein, which includes a classification of Sam's 1996, estimated 1997 and budgeted 1998 expenses by major category; and (probably unnecessarily) a Peat Marwick letter of 10/23/96 about IRS expense documentation standards. Please note that Sam's expense statement for 9/1/97 –12/31/97 has not yet been received.

PB/c

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ImClone Systems Incorporated

Meeting of the Executive Committee of the Board of Directors

October 14, 1998

A meeting of the Executive Committee of the Board of Directors of ImClone Systems Incorporated (the "Company") was held pursuant to notice duly given via teleconference on October 14, 1998. Present at the meeting were the following members of the Executive Committee: Robert F. Goldhammer (Chairman) and Samuel D. Waksal. Harlan W. Waksal recused himself from the meeting due to his interest in the subject matter.

The meeting was called to discuss a potential short-term loan of $100,000 to Harlan W. Waksal. After discussion duly had, such loan, on substantially the terms of the promissory note attached hereto, was approved.

There being no further business to come before the committee, a motion to adjourn the meeting was made, seconded and so voted and the meeting was declared adjourned.

A true and accurate record

Attest: Robert F. Goldhammer
Robert F. Goldhammer
Chairman

PROMISSORY NOTE

Date: October 15, 1998
New York, New York

FOR VALUE RECEIVED, the undersigned, Harlan W. Waksal, residing at 85 Stonebridge Road, Montclair, New Jersey, 07042, hereby promises to pay to the order of ImClone Systems Incorporated, 180 Varick Street, New York, New York, 10014, on demand the principal sum of $100,000.00, and to pay interest on the unpaid principal sum for the period that the loan is outstanding, on the maturity hereof, at the rate per annum equal to the prime or base rate announced by Chase Bank, N.A., at its offices in New York, New York on the date hereof, but not less than the Federal short-term rate, as defined in Section 1274(d) of the Internal Revenue Code of 1986, as amended.

It is the intent of the undersigned to pay the principal within thirty (30) days of the date hereof, by which time certain shares of ImClone Common Stock underlying warrants held by the undersigned are expected to be registered with the U.S. Securities and Exchange Commission, thus removing restrictions in connection therewith. Right to extend the maturity beyond that date will require the approval of the full ImClone Board of Directors.

Chase Prime Rate Inquiry Phone # is 212-270-7440.

8¼% on 10/15/98
(Changed to 8% on 10/

In the event that:

(i) the undersigned shall fail to pay any installment of interest within ten (10) business days after such installment is due; or

(ii) the undersigned shall become insolvent, have any action commenced against it under any bankruptcy, insolvency or similar statute, or take any action for relief under any bankruptcy, insolvency or similar statute;

then the holder of this Note, by notice to the undersigned, shall be entitled to declare the entire unpaid balance of this Note (together with interest accrued thereon) to be immediately due and payable in full, except that no such notice or declaration shall be required if an event described in

clause (ii) above shall have occurred, in which case the entire unpaid balance of this Note, together with interest accrued thereon, shall be immediately due and payable.

Presentment for payment, notice of dishonor, protest and notice of protest are hereby expressly waived.

The undersigned may prepay this Note in whole or in part at any time and from time to time.

This Note is executed under, and is to be construed in accordance with the laws of, the State of New York.

IN WITNESS WHEREOF, the undersigned has duly executed this Note as of the day and year first above stated.

Harlan W. Waksal

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ImClone Systems Incorporated

Meeting of the Audit Committee of the Board of Directors

November 2, 1998

Pursuant to notice duly given, a meeting of the Audit Committee (the "Committee") of the Board of Directors was held on November 2, 1998 at the executive offices of the Company located at 180 Varick Street, 7th Floor, New York, New York held immediately after the Board of Directors meeting. Present were the following members of the Committee: Paul B. Kopperl (Chairman); David M. Kies , Vincent T. DeVita, and William Miller. Also attending were the following non-Committee members: Robert F. Goldhammer, Carl S. Goldfischer, Samuel D. Waksal (for portions of the meeting), Harlan W. Waksal, John B. Landes, Paul A. Goldstein a well as John Capecci, Gerry Norcott and Mark Thomas of KPMG Peat Marwick LLP, the Company's independent auditors ("KPMG").

The meeting followed the previously distributed agenda (attached hereto) and began by introducing the members of the KPMG audit team, including the new engagement partner on th account, John Capecci, who is replacing the prior engagement partner, Gerry Norcott. KPMG explained that the transition was required because Mr. Norcott is moving to another role within KPMG. Mr. Capecci described his auditing background with KPMG which included auditing life science companies.

The auditors set forth the elements of its 1998 audit plan for the Company and the timin of its intended audit procedures. Discussion turned to the Company's plans for assessing the Y2K issue. KPMG indicated that the handling of the Y2K issue by their audit clients would be part of each 1998 audit. KPMG stated that they would not test the Company's systems, but that

the status, implementation and disclosure in reporting documents of the Company's Y2K plans would be a factor considered by the auditors in the issuance of an unqualified going concern opinion for the Company. The last point will be addressed in KPMG's 1999 engagement letter. KPMG undertook to deliver a copy of its Y2K questionnaire to the Company for distribution to management and the Committee. In this connection, management pointed out that (1) ImClone is able in good faith to make the Y2K statements required by the SEC in the 3Q98 and subsequent filings and (2) the Company is already testing its Y2K compliance at its Branchburg clinical manufacturing facility.

KPMG also discussed general financial reporting developments, including the continued focus of the FASB on interpretation of stock option accounting. KPMG will continue to keep the Company apprised of these and other relevant FASB developments.

The auditors then left the meeting.

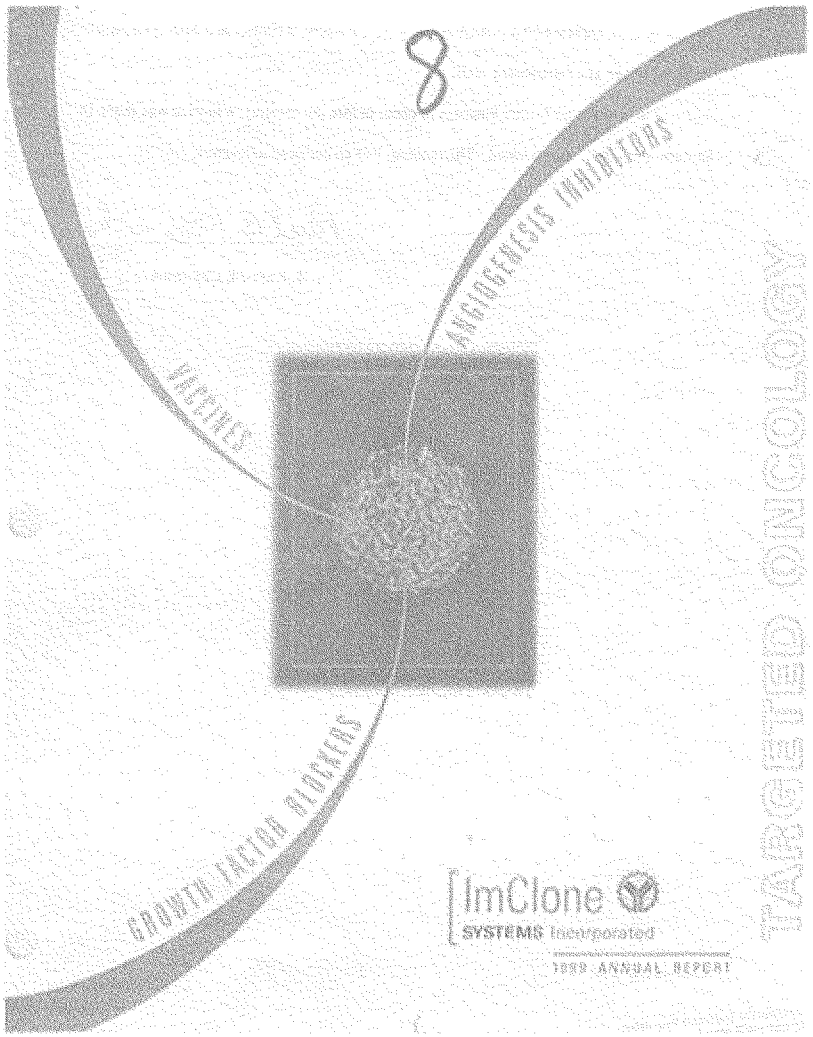
The meeting continued with the discussion of the handling of expense reports of the Company's Chief Executive Officer, Dr. Sam Waksal. Dr. Goldfischer and Mr. Goldhammmer, who are responsible for reviewing the CEO's expense reimbursement invoices, discussed with the Committee the current status of the CEO's adherence to the February 12,1998 guidelines of the Committee in this regard, in particular that documentation with respect to the breakdown and nature of these expenses was being timely provided, and that the practice is being followed for no reimbursement to be paid until expense invoices are properly documented. However certain expenditures have been flagged for further description and resubmission before money is to be reimbursed.

The Committee discussed the current status of the financial controls of the Company. Harlan Waksal expressed his confidence that the Company's control and MIS systems are in excellent shape and functioning well.

There being no further business to come before the meeting, a motion was made to adjourn, seconded, and so voted. The meeting was so declared adjourned.

Paul B. Kopperl

Paul B. Kopperl, Chairman


8
ANGIOGENESIS INHIBITORS
VACCINES
GROWTH FACTOR BLOCKERS
TARGETED ONCOLOGY
ImClone
SYSTEMS Incorporated
1998 ANNUAL REPORT

TO OUR SHAREHOLDERS

growth factor blockers
angiogenesis inhibitors
vaccines

IT IS WITH GREAT PLEASURE THAT WE REVIEW FOR YOU OUR 1999 FISCAL YEAR. FOR SHAREHOLDERS AND EMPLOYEES OF IMCLONE SYSTEMS INCORPORATED, IT WAS A SEMINAL YEAR FILLED WITH PROUD ACHIEVEMENTS. IN EVERY AREA OF THE COMPANY'S ENDEAVORS SIGNIFICANT GROWTH OCCURRED, SETTING THE STAGE FOR OUR FUTURE SUCCESS.

During the last year, ImClone Systems made notable progress in several areas including our clinical development and research programs. The scientific advancements made throughout this year enabled ImClone Systems to raise substantial capital. This has given us the strong financial resources to put in place expertise that can lead us to the commercialization of our first product, a targeted biologic cancer therapy.

PRODUCT DEVELOPMENT PROGRAMS

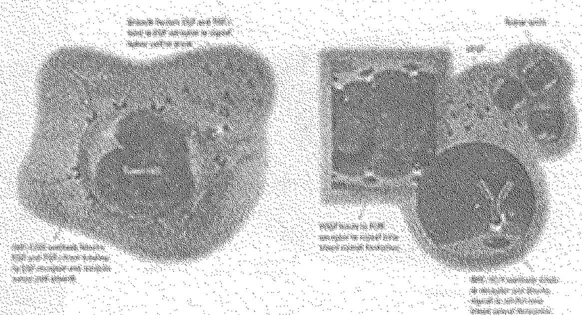
Our research and development programs, which include growth factor blockers, anti-angiogenesis drugs and cancer vaccines, collectively represent some of the most exciting approaches in drug development in the field of oncology today. We are developing an array of biologic therapies that specifically target and inhibit cancer causing mechanisms. We believe this targeted approach will improve disease management and the quality of life of patients with a variety of cancers. It is our goal to become a leader in the field of targeted oncology.

Our lead product in clinical development, IMC-C225, is a monoclonal antibody that blocks the ability of Epidermal Growth Factor to bind to its receptor (EGFr). IMC-C225 blocks the signal that allows tumor cells to grow, divide and repair. As EGFr is over expressed on approximately one-third of all solid tumors, IMC-C225 potentially has broad therapeutic application in a variety of cancers.

IMC-C225 has been in clinical trials since 1995. In two early phase I/II clinical trials of IMC-C225 in patients with advanced or refractory head and neck carcinoma, findings demonstrated strong evidence of the antibody's biologic activity in combination with radiation therapy and in combination with chemotherapy. These trials identified head and neck carcinoma as a key indication for moving IMC-C225 through the regulatory approval process toward commercialization.


IMCLONE
SYSTEMS
INCORPORATED

IMC-C225 IMC-1C11



IMCLONE SYSTEMS PARTNERSHIPS

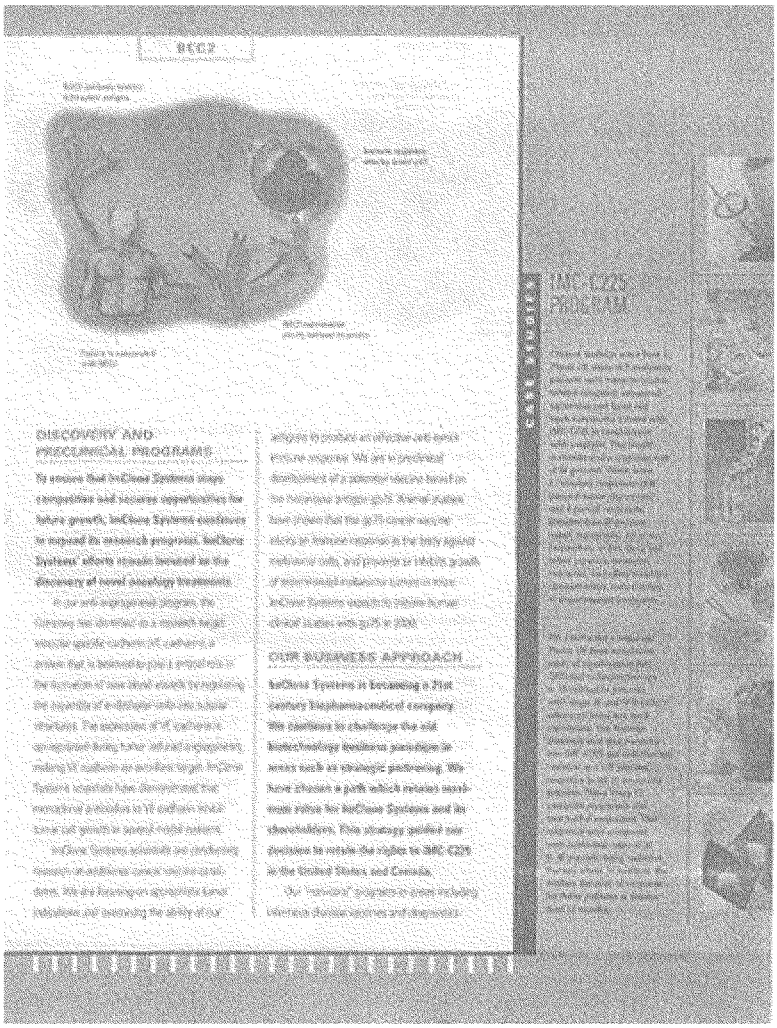
IMC-C225 — Merck KGaA

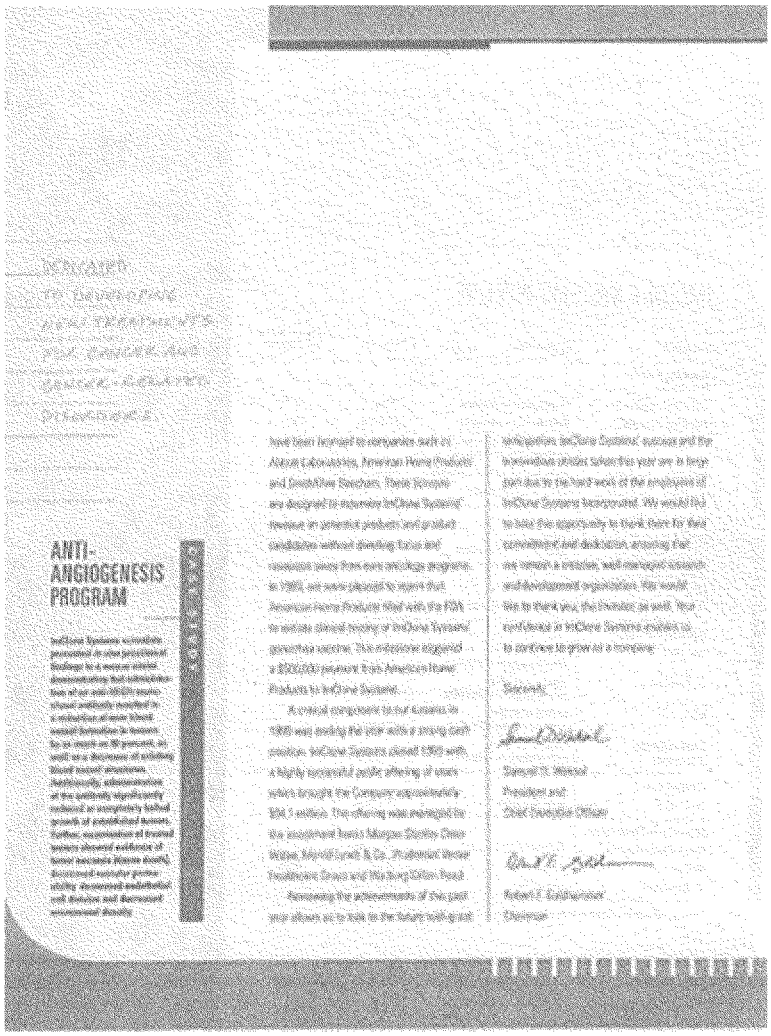
[illegible]

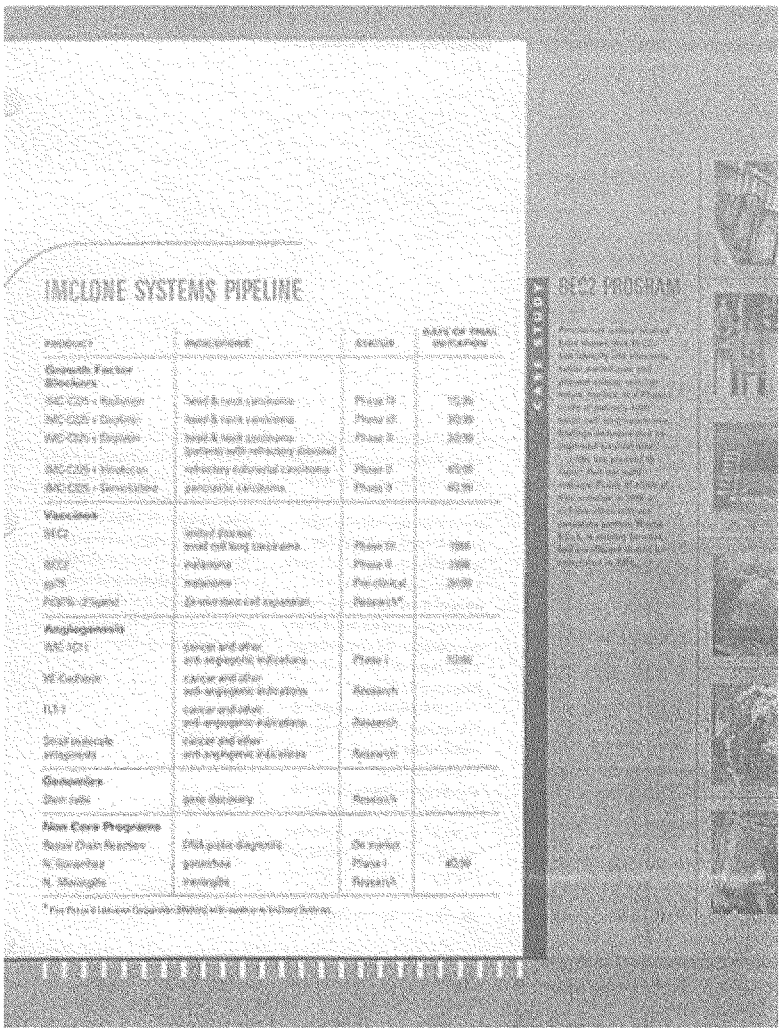
BEC2 — Merck KGaA

[illegible]

[illegible]


BEC2
CASE STUDIES
IMC-C225 PROGRAM
DISCOVERY AND PRECLINICAL PROGRAMS
OUR BUSINESS APPROACH


ANTI-
ANGIOGENESIS
PROGRAM



IMCLONE SYSTEMS PIPELINE

Product	Indication	Status	Date of First Launch
Growth Factor Blockers			
IMC-C225 + Radiation	head & neck carcinoma	Phase III	1Q'06
IMC-C225 + Cisplatin	head & neck carcinoma	Phase III	2Q'06
IMC-C225 + Taxotere	head & neck carcinoma (patients with refractory disease)	Phase III	3Q'06
IMC-C225 + Irinotecan	refractory colorectal carcinoma	Phase II	4Q'06
IMC-C225 + Gemcitabine	pancreatic carcinoma	Phase II	4Q'06
Vaccines			
BEC2	active immune adjuvant therapy small cell lung carcinoma	Phase III	1Q'06
BEC2	melanoma	Phase II	1Q'06
oncoVAX	melanoma	Pre-clinical	2Q'06
FGFR3 - Fusion	Bladder cancer cell expression	Research*	
Angiogenesis			
IMC-1121	cancer and other anti-angiogenic indications	Phase I	4Q'06
VE-Cadherin	cancer and other anti-angiogenic indications	Research	
ILY-1	cancer and other anti-angiogenic indications	Research	
Small molecule integrins	cancer and other anti-angiogenic indications	Research	
Oncogenes			
Stem cells	gene discovery	Research	
Non-Core Programs			
Tumor Chain Reaction	DNA-polio diagnostic	On market	
K-Statin/Tet	prevention	Phase I	4Q'06
K-Statin/Rx	therapeutic	Research	

* For Phase II trials in bladder cancer, ImClone is working with partners in Europe and Asia.

CASE STUDY

BEC2 PROGRAM

OFFICERS

Lee E.D. Walker, Ph.D.
President
Chief Executive Officer

Elaine M. Walker, M.D.
Executive Vice President
Chief Operating Officer

Carl E. Gustafson, M.D.
Vice President
Finance, Chief Financial Officer

John R. Lemke
Vice President
Business Development
and General Counsel

Ronald A. Merrill
Vice President
Marketing and Sales

S. Joseph Tarnowski, Ph.D.
Vice President
Product and Process Development

Michael Peterson, Ph.D.
Vice President
Discovery Research

Peter Barlow, Ph.D.
Vice President
Research

Richard A. Tegard
Vice President,
Regulatory Affairs and
Quality Assurance

BOARD OF DIRECTORS

Robert T. Gallagher
Chairman of the Board

Richard Roth
Former Chairman of the Board
Kleiner Perkins Caufield & Byers

Edward L. Cahill, Jr., M.D.
Chief, Pediatrics
San Dimas Community Hospital

Ronald M. Nimi
Partner, Cahill & Gordon

Fred H. Nugent
Retired Chairman and CEO,
Nugent Insurance, Inc.

Alan Mendelson, M.D.
President, MD Anderson Cancer
Center, University of Texas

William R. Miller
Senior Vice Chairman
of the Board of Directors,
SmithKline Beecham Corporation

Evelyn M. Witkin, M.D.
Executive Vice President and
Chief Operating Officer,
Public Health Research Institute

Samuel B. Weiss, Ph.D.
Professor and Chairman (Retired)
Cellular Systems Incorporated

SCIENTIFIC ADVISORY BOARD

Thomas Steitz, Ph.D.
Chairman, Scientific Advisory Board
Professor of Molecular Biology,
Professor, Chemistry, Yale Univ.
Career Investigator, Howard
Hughes Medical Institute

Thomas Kunkel, M.D.
Professor of Medicine, Division of
the Chemistry of Genetic Regulation,
Harvard Medical School

Charles A. Dinarello, M.D.
Professor of Medicine, University
of Colorado School of Medicine

Michael Feldman, Ph.D.
Vice President, Discovery Research,
Cellular Systems Incorporated;
Member of the Israeli Academy
of Sciences and Humanities
and the National Academy of Arts
and Sciences

Jo Milne, M.D.
Chairman of the Department of
Radiation Oncology, Memorial
Sloan-Kettering Cancer Center

Daniel T. Kenedi, M.D.
Professor and Head of the Division
of Geographic Medicine and
Infectious Diseases, Tufts University
School of Medicine

Ann M. Arvin, Ph.D.
Professor, The Stanford University

Jane Henderson, M.D.
President, MD Anderson Cancer
Center, Orlando at Texas

Malcolm Moore, Ph.D.
Head, Tissue Regulation
Laboratory, Chief of the Stem
Cell Biology and Development
Service, Memorial Sloan-Kettering
Cancer Center

Richard Mulligan, Ph.D.
Member of the Institute of Genetics,
Harvard Medical School;
Investigator, Howard Hughes Medical
Institute and Children's
Hospital, Boston

Robert Schneider, Ph.D.
Associate Professor, Department of
Biochemistry, New York University
Medical Center

W. Frederick Sperling, M.D.
J. Herbert Bate Professor of
Medicine and Microbiology and
Immunology, University of North
Carolina School of Medicine

Samuel D. Waksal, Ph.D.
President and Chief Executive
Officer, ImClone Systems
Incorporated

CORPORATE AND OPERATIONS

Corporate Headquarters
180 Varick Street
New York, New York 10014
Tel: 212 645 1405
Fax: 212 645 2054

Branchburg Manufacturing Facility
29 Emmons Drive
Commons Way
Branchburg, New Jersey 08876
Tel: 908 707 1500
Fax: 908 704 0037

TRANSFER AGENT AND REGISTRAR

Stockholder inquiries should be directed to:
ImClone Systems Incorporated
Investor Relations
180 Varick Street
New York, New York 10014
Tel: 212 645 1405
Fax: 212 645 2054

CERTIFIED PUBLIC ACCOUNTANTS

KPMG LLP
Princeton, New Jersey

COMMON STOCK

ImClone Systems Incorporated is traded on the NASDAQ National Market under the symbol IMCL. The following table sets forth the high and low sale prices for the indicated periods. The stock price ranges are as of December 31, 1995.

	High	Low
First Quarter	11 1/2	8
Second Quarter	13	10 1/4
Third Quarter	18 1/4	11 3/4
Fourth Quarter	18 3/4	15 1/2

COMPANY REPORTS

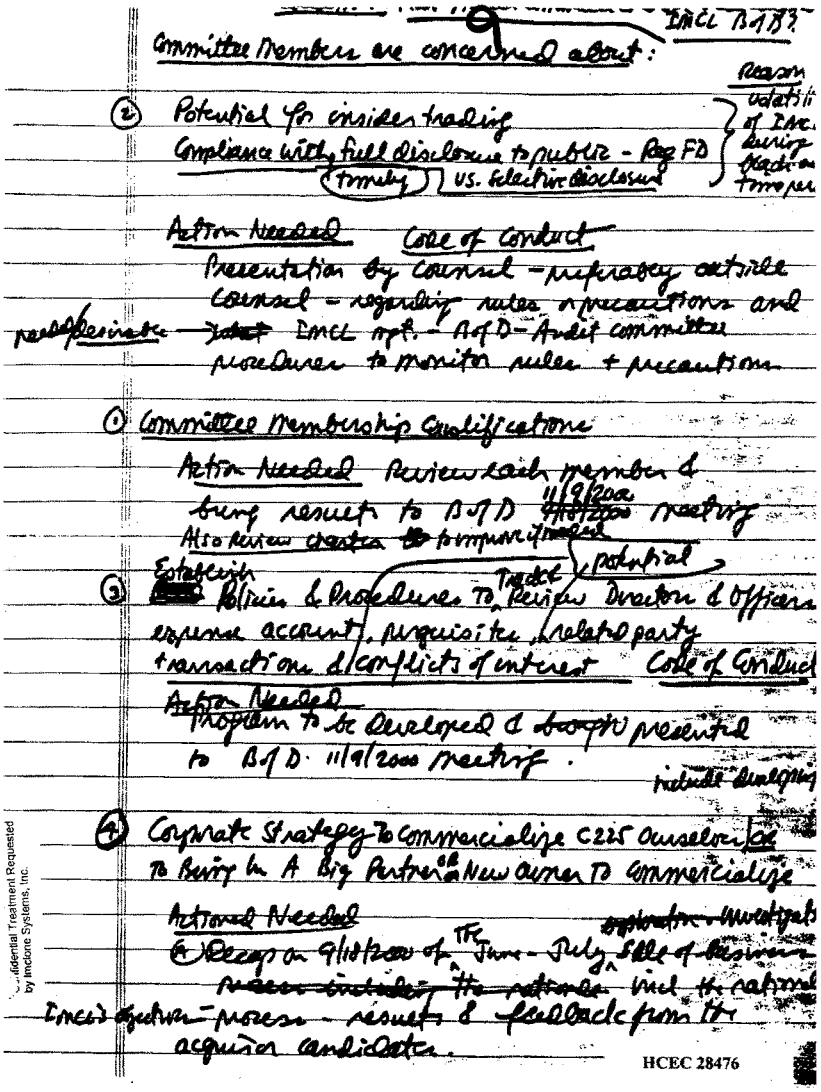
For additional information concerning the Company, including copies of any exhibits listed in this annual report upon payment to the Company of its reasonable expenses in furnishing such exhibits, please contact:

Andrew F. Ashley, Esq.
Assistant Vice President
Corporate Counsel, Secretary
ImClone Systems Incorporated
180 Varick Street
New York, New York 10014
Tel: 212 645 1405
Fax: 212 645 2054

ANNUAL MEETING

The Annual Meeting of Stockholders will be held at:
The Yale Club of New York City
50 Vanderbilt Avenue
New York, NY 10017
May 21, 1996 at 10:00 A.M.

Design: Sullivan Perkins, New York
Illustrations: Lorraine Hammond,
Arlington, Vermont



IMCL Audit?

Committee Members are concerned about:

Reason volatility of IMC during fraction improper

② Potential for insider trading
Compliance with full Disclosure to public - Reg FD
(timely) US. selective disclosure

Action Needed Code of Conduct
Presentation by Counsel - preparer outside Counsel - regarding rules precautions and perspective → IMCL rpt. - BofD - Audit committee procedures to monitor rules + precautions

① Committee Membership Qualifications
Action Needed Review each member & bring results to BofD 11/9/2000 meeting
Also review charter for compliance

③ Establish Policies & Procedures to Review Director & Officers (potential) expense account, perquisites, related party transactions & conflicts of interest Code of Conduct
Action Needed
Program to be developed & charter presented to BofD 11/9/2000 meeting.
include disclosure

④ Corporate Strategy to Commercialize C225 Ourselves OR To Bring in A Big Partner OR New Owner To Commercialize
Actions Needed
⑤ Recap on 9/10/2000 of the June - July Sale of Business exploration - investigate process including the rationale and the rationale used the rationale IMCL's decision - process - results & feedback from the acquirer candidates.

Page 2

④ Continued

(A) Discussion on 9/18/2000 of ImClone's commercialization plans vs. contingencies & risks

(i) Review production vol. + unit cost vs. varying projected sales volumes

(ii) Discussion & assessment of risks

⑤ Contingent Planning for Management Succession

What are we prepared to do if the CEO or the COO is incapacitated or killed? In an HBS article Bartlett, what do you do when the CEO becomes VP?

⑥ Plans for CFO

Job description

Process

In Summary

A. Regulatory issues & compliance

B. Audit Committee membership & charter

C. Corp governance

D. Management development & succession

E. Corporate strategy

10

PAUL, WEISS, RIFKIND, WHARTON & GARRISON
1285 AVENUE OF THE AMERICAS, NEW YORK, N.Y. 10019-6064 (212) 373-3000

FAX COVER SHEET

FROM: Saul H. Finkelstein
DATE: January 14, 2002
RETURN FAX NUMBER: 212-373-2053
TOTAL NUMBER OF PAGES: 3 (Including Cover Sheet)

NAME	FIRM/COMPANY	FAX NO. (PLEASE VERIFY NUMBER)	TIME SENT
Catherine M. Vaczy	ImClone Systems Incorporated	212-645-2770	

If transmission is incomplete, please call: 212-373-3280 Operator:

RETURN ORIGINAL TO: [X] SENDER [ ] RECORDS

COMMENTS:

Issuer's Letter

November 10, 2000

Bank of America, N.A.
101 South Tryon Street
Charlotte, North Carolina 28255

Re: Proposed Pledge of Stock of ImClone Systems Incorporated by Samuel D. Waksal

Ladies and Gentlemen:

ImClone Systems Incorporated (the "Issuer") understands that Samuel D. Waksal (the "Pledgor") proposes to enter into a credit transaction with Bank of America, N.A. (the "Bank") whereby a certain warrant (the "Warrant") owned by the Pledgor to purchase 350,000 shares (the "Shares") of common stock of the Issuer owned by the Pledgor will be pledged to the Bank as security for the obligations of Pledgor to the Bank (the "Pledge").

The Issuer hereby certifies to the Bank as follows:

(a) as of the date hereof, the Pledgor is an "affiliate" of the Issuer within the meaning of Rule 144 ("Rule 144") promulgated pursuant to the Securities Act of 1933, as amended (the "Act");
(b) the "restricted" common stock of the Issuer (as such term is defined in Rule 144) owned by the Pledgor and described on Exhibit "A" has been owned by the Pledgor since the date noted next to such shares on such Exhibit and has been fully paid for in cash;
(c) as of the date hereof, none of the shares of the common stock of the Issuer owned by Pledgor were issued to Pledgor in connection with a merger, acquisition or similar transaction which would make such shares subject to resale restrictions under Rule 145 promulgated pursuant to the Securities Act of 1933, as amended, except as noted on Exhibit "A";
(d) the Issuer has no objection to the Pledge and confirms that to the best of its knowledge the Pledgor will not violate any insider trading or other policy or rule of the Issuer;
(e) all shares of common stock subject to options granted by the Issuer to the Pledgor are subject to one or more effective registration statements on Form S-8 (collectively, the "Registration Statement") under the Act and may be sold by the Pledgor or the Bank pursuant thereto, and
(f) the sales of the following persons or entities or persons will be aggregated with sales of the Pledgor for purposes of determining compliance with the volume limitations of Rule 144:

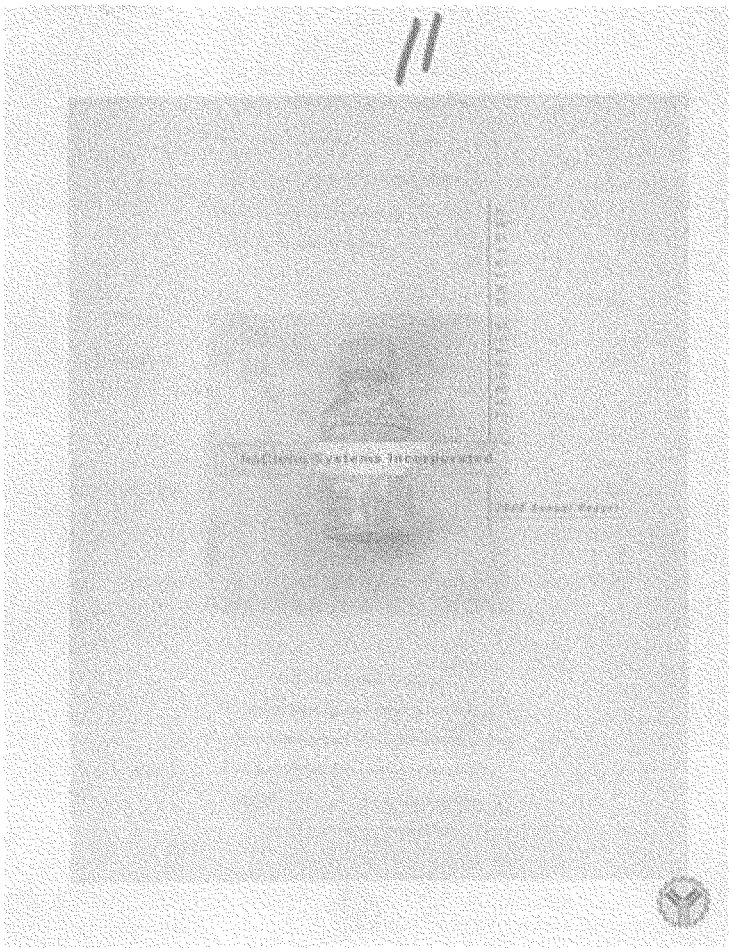
The Issuer hereby agrees that if the Bank forecloses on, or wishes to sell or otherwise dispose of, the Warrant subject to the Pledge or the Shares as a result of a default by the Pledgor, the Issuer shall, notwithstanding any policy or procedure that Issuer may have in place at such time that would prevent or delay any sale or transfer of the Warrant or the Shares by the Pledgor as of the date of the Pledge or at the time of such foreclosure, cooperate with the Bank to promptly effect the foreclosure or sale or other disposition of the Warrant or the Shares in accordance with applicable law, whether in the name of Pledgor, Bank or a nominee of the Bank including without limitation, (i) to issue within five (5) days after request from the Bank and submission of required documentation by or on behalf of the Bank such opinions, instructions or other approvals as may be required to authorize the Transfer Agent to register the transfer of the Warrant or the Shares in connection with any such foreclosure or sale or other disposition of the Warrant or the Shares by the Bank, (ii) to remove any legends thereon, or (iii) to provide the Bank or any broker or other agent of the Bank promptly upon request any information reasonably requested by the Bank or such broker with respect to any proposed sale, or foreclosure or other disposition of the Warrant or the Shares. Notwithstanding the foregoing, the Issuer shall not be required to take any action which in the reasonable opinion of the Issuer and its counsel would result in the violation of any applicable laws.

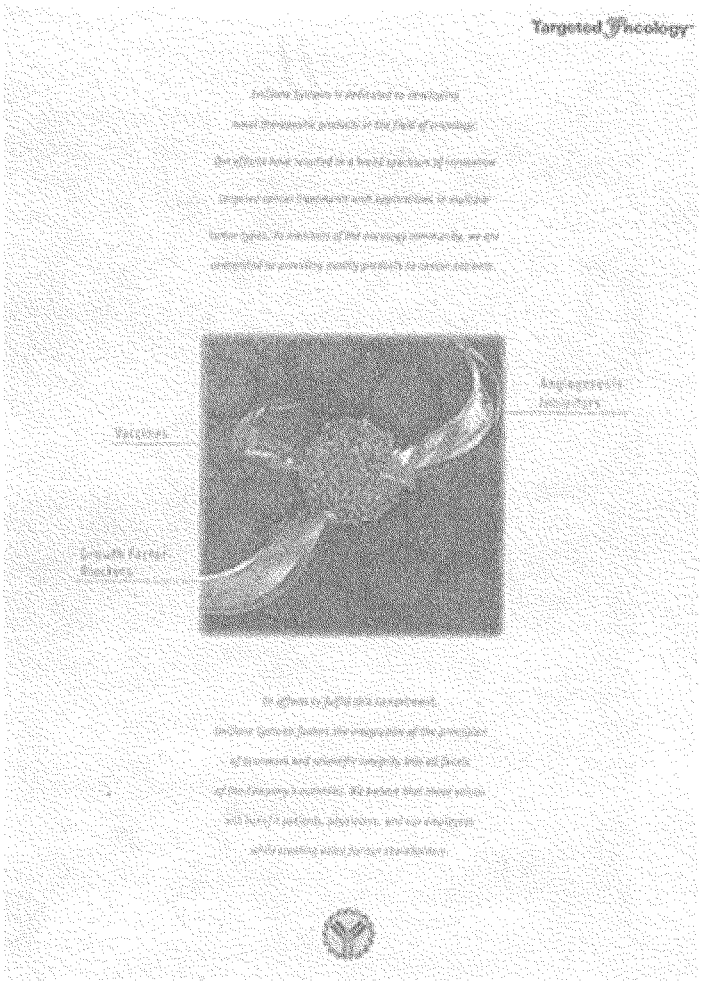
The Issuer also agrees that (i) the Issuer will use its reasonable best efforts to maintain the effectiveness of the Registration Statement at all times that the Pledge is in effect, including the filing of any post-effective amendments to the Registration Statement or taking other actions as may be reasonably requested by the Pledgor or the Bank, (ii) the Issuer will notify the Bank of any stop order issued with respect to the Registration Statement and will use its best efforts to remove any such stop order and (iii) upon the request of the Bank, it shall promptly issue, or cause its counsel to issue, any necessary opinions to enable the transfer agent to remove any legends on the certificates subject to the Pledge upon the expiration of any requires holding periods to the extent that the Issuer or its counsel determines that such removal will not violate applicable law.

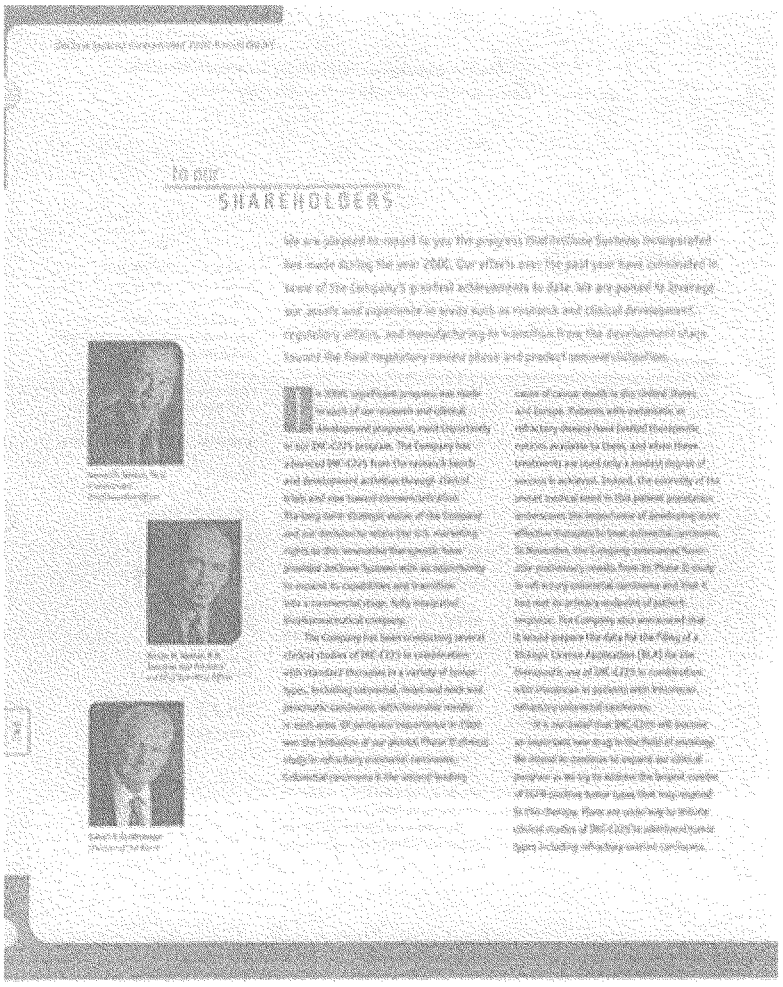
The Issuer acknowledges that the Bank will be relying on the Issuer's representations and agreements set forth in this letter.

IMCLONE SYSTEMS INCORPORATED

By: _____
Name: [illegible]
Title: General Counsel




Targeted Oncology



TO OUR
SHAREHOLDERS

We are pleased to report to you the progress that InCline Therapeutics Incorporated has made during the year 2008. Our efforts over the past year have culminated in some of the Company's greatest achievements to date. We are poised to leverage our assets and experience in areas such as research and clinical development, regulatory affairs, and manufacturing to transition from the development stage toward the final regulatory review phase and product commercialization.


VISION
"As we look forward, long-term vision and our decision to return U.S. marketing rights
to ONCOLYS have provided us with an opportunity to expand our capabilities and
transition from a commercial stage, fully integrated biopharmaceutical company."


clinical affairs
NEXT GENERATION TREATMENTS

of IMC-C225 in combination with radiotherapy as first line treatment for head and neck carcinoma. Planning is underway to initiate a Phase III clinical trial of IMC-C225 in combination with cisplatin and 5FU as first line treatment in patients with colorectal carcinoma.

IMC-1C11

The Company's lead angiogenesis inhibitor, IMC-1C11, is an investigational monoclonal antibody that binds with high affinity to the vascular endothelial growth factor receptor (VEGFR), known as KDR. By binding to KDR, IMC-1C11 blocks the ability of VEGF from initiating receptor activation, thereby inhibiting angiogenesis.

The Company is currently conducting a Phase I clinical study to evaluate the safety and pharmacokinetics of IMC-1C11 in patients with metastatic colorectal carcinoma. Commencement of patient treatment occurred in June 2000 and the study is expected to be completed in the second half of 2001.

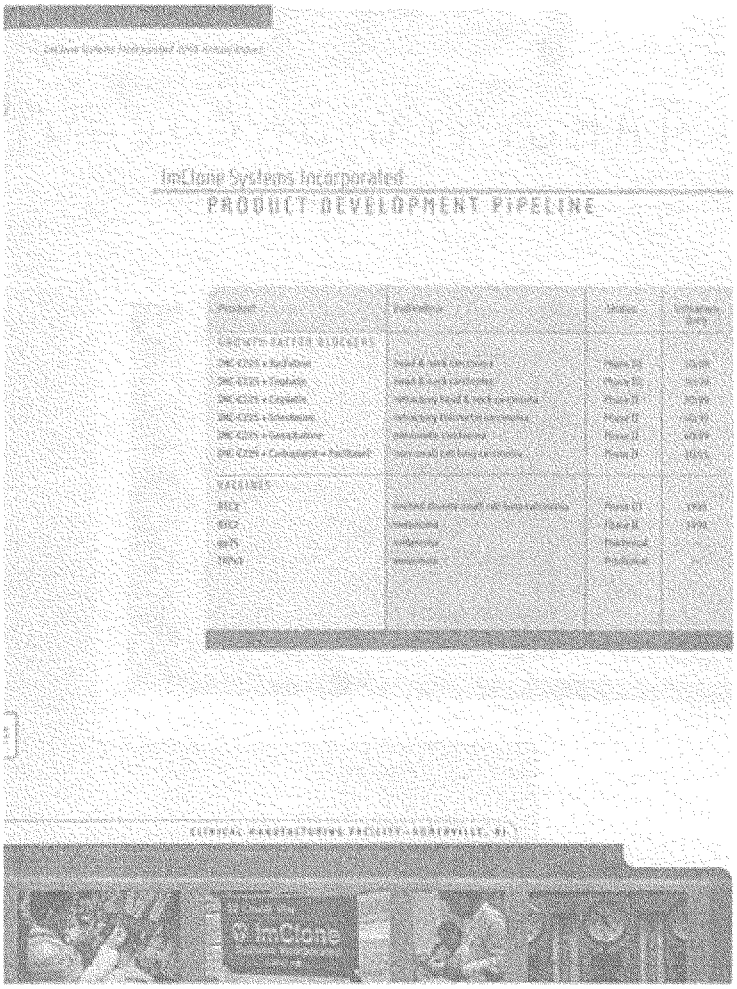
3B6.2

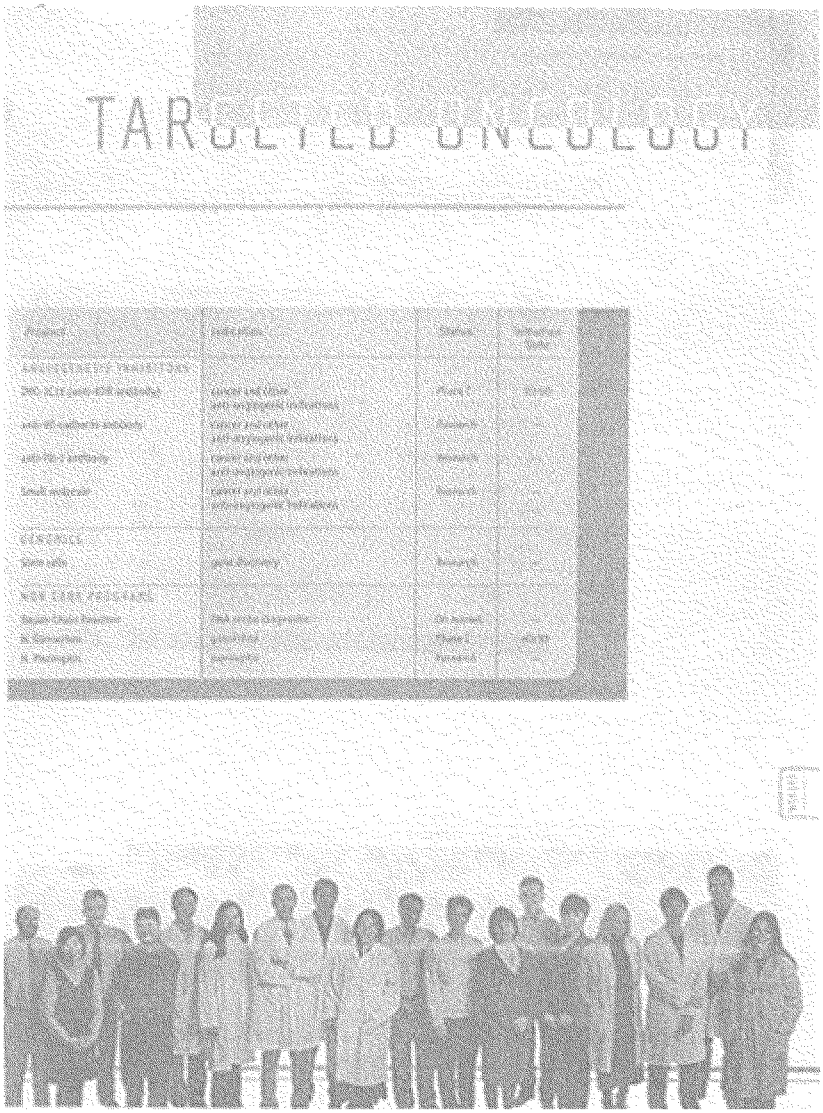
3B6.2 is an investigational monoclonal antibody designed to prevent or delay the recurrence of certain types of cancer. The 3B6.2 antibody attacks the ganglioside GD2, a tumor-associated antigen on the surface of certain types of cancer cells. By attacking this antigen, 3B6.2 administered in combination with the immune stimulant BCG, appears to elicit a stronger immune response than that of natural GD2.

The multinational 170-patient Phase III clinical trial evaluating 3B6.2 in patients with limited disease small cell lung carcinoma is expected to reach the halfway point in patient recruitment in the first half of 2001. The study evaluating patient survival is expected to be fully enrolled by 2003. Following completion of patient enrollment, the study will take approximately one year to complete, with data expected to be available in 2004.

The Company is also conducting a Phase II study of 3B6.2 in malignant melanoma. Enrollment for the study is complete and patient treatment is ongoing.


SUCCESS
marketing & sales
BECOMING FULLY INTEGRATED


ImClone Systems Incorporated
PRODUCT DEVELOPMENT PIPELINE
Product
Indication
Status
Launch Year
CANCER THERAPEUTICS
VASCULAR
ImClone


TARGETED ONCOLOGY

OFFICERS

Samuel D. Waksal, Ph.D. (center)
President
Chief Executive Officer

Harlan W. Waksal, M.D.
Executive Vice President
Chief Operating Officer

Peter Ashton, Ph.D.
Senior Vice President
Research

John A. Landon, Esq.
Senior Vice President
Legal

Charles Moore
Vice President
MIS and Facilities

Paul A. Fonteyne, CPA
Vice President
Financial Operations

Ronald A. Martell
Vice President
Marketing and Sales

Nu Rahr H. Mordoh, M.D.
Vice President
Clinical Affairs

Larry Pardue
Vice President
Engineering and
Facilities

Andrew F. Ramsay, Esq.
Vice President
Corporate
Communications

S. Joseph Sirowatka, Ph.D.
Vice President
Product and Process
Development

Catherine M. Young, Esq.
Vice President
Legal

Larry White, Ph.D.
Vice President
Research

BOARD OF DIRECTORS

Robert F. Goldhammer
Chairman
Partner, Oxford Investments

Richard Barth
Senior Chairman
of the Board
Old Lyme, CT

Vincent T. DeVita, Jr., M.D.
Executive Director
Yale Cancer Center

David M. Kies, Esq.
Partner
Sullivan & Cromwell

Paul B. Kopperl
President
Kopperl Investments, Inc.

Robert S. Kopperl, Esq.
Partner, Sullivan & Cromwell

Ronald B. Lazarus, Ph.D.
President
The Rockefeller University

John Mendelsohn, M.D.
President
MD Anderson Cancer Center
University of Texas

William B. Miller
Senior Vice Chairman
of the Board
Bristol-Myers Squibb
Company

Harlan W. Waksal, M.D.
Executive Vice President and
Chief Operating Officer
ImClone Systems
Incorporated

Samuel D. Waksal, Ph.D.
President and CEO
ImClone Systems
Incorporated

Standing (L-R): Robert F. Goldhammer, Richard Barth, Harlan W. Waksal, Vincent T. DeVita, Jr., David M. Kies, John Mendelsohn, Robert S. Kopperl, Paul B. Kopperl, Samuel D. Waksal, Ronald B. Lazarus, William B. Miller

Seated (L-R): Harlan W. Waksal, Samuel D. Waksal

SCIENTIFIC ADVISORY BOARD

Vincent T. DeVita, Jr., M.D.
Chairman
Professor of Medicine and Yale
Cancer Center Scientific
Director
Yale University School
of Medicine

Steven A. Rosenberg, M.D., Ph.D.
Chief, Surgery Branch
National Cancer Institute

Samuel Broder, M.D.
Director
National Cancer Institute

Thomas Evans, M.D.
Professor of Medicine
Director of the Division
of Renal Medicine
Harvard Medical School

Joseph T. Bruder, M.D.
Professor of Medicine
Director of the Division
of Renal Medicine
Harvard Medical School

Jo Ivey Boufford, M.D.
Dean
New York University
College of Nursing

Gerald T. Evans, M.D.
Professor and Head of
the Division of Diagnostic
Oncology and Therapeutic
Research
Duke University School
of Medicine

Kenneth B. Taylor, Ph.D.
Professor
The Rockefeller University

John Mendelsohn, M.D.
President
MD Anderson Cancer Center
University of Texas

Malcolm Moore, Ph.D.
Ludwig Professor of
Cell Biology, Head of the
Stem Cell Laboratory
Memorial Sloan-Kettering
Cancer Center

Richard Pestell, Ph.D.
Professor of Genetics
Director, Breast Cancer
Program
Kimmel Cancer Institute
Thomas Jefferson
University

Frederick Sperling, M.D.
J. Herbert Bon Professor
of Medicine and
Microbiology and
Immunology
University of North Carolina
School of Medicine

Samuel D. Waksal, Ph.D.
President and CEO
ImClone Systems
Incorporated

CORPORATE INFORMATION

Corporate Headquarters
140 Wall Street
New York, New York 10004
Tel: 212.645.1405
Fax: 212.645.2054

Brandsbury
Manufacturing Facility
22 Chalk Way
Somerville, New Jersey 08876
Tel: 908.218.9588
Fax: 908.704.8375

www.brandsbury.com

TRANSFER AGENT AND REGISTRAR

Stockholder inquiries should be directed to:
State Street Bank & Trust Company
c/o EquiServe
P.O. Box 43011
Providence, RI 02940-3011
Tel: 1.800.426.5523
http://www.equiserve.com

CERTIFIED PUBLIC ACCOUNTANTS

KPMG LLP
Princeton, New Jersey

COMMON STOCK

Dr Chase Systems, Incorporated is traded on the NASDAQ National Market under the symbol: DRCL.

The following table sets forth the high and low sale prices for the Company's common stock for the fiscal year ended December 31, 2006. These prices, shown as adjusted for a 3-for-2 split of Retail on the first of February in October 2006.

	High	Low
1st Quarter	$61.99	$12.00
2nd Quarter	$52.41	$35.01
3rd Quarter	$62.96	$36.75
4th Quarter	$69.13	$30.05

COMPANY REPORTS

For additional information or comments of the Company, including copies of any exhibits listed in this annual report upon payment to the Company of its reasonable expenses in furnishing such exhibits, please contact:

Andrea E. Bailey, Esq.
Vice President
Corporate Communications
Dr Chase Systems, Incorporated
140 Wall Street
New York, New York 10004
Tel: 212.645.1405
Fax: 212.645.2054

ANNUAL MEETING

The Annual Meeting of Stockholders will be held at:
Le Parker Meridien Hotel
New York
118 West 57th Street
New York, NY 10019
May 24, 2007 at 10:00 a.m.

Risk annual report on Form 10-K and [illegible] statements, other information, and news re[illegible] Dr Chase and its subsidiaries, is filed with the Securities and Exchange Commission on Form 10-K.

Design: Collaborative, New York
www.collab.com

Photography: Richard Ford, Hoboken, NJ

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ImClone Systems Incorporated

Special Meeting of the Executive Committee
of the Board of Directors

February 20, 2001

A special meeting of the Executive Committee of the Board of Directors (the "Committee") of ImClone Systems Incorporated (the "Company") was held via teleconference at approximately 6 :00 on Tuesday, February 20, 2001.

In attendance at the meeting were Dr. Harlan W. Waksal and Mr. Robert F. Goldhammer, constituting two of the three members of the Committee. Dr. Samuel Waksal, the third member of the Committee, recused himself due to the subject matter of the meeting.

The subject of the meeting related to the Company's making a loan to Dr. Samuel Waksal in the amount of $282,200. After due discussion, the Committee ratified the making of the loan to Dr. Samuel D. Waksal and the form of the Promissory Note attached hereto as Attachment A.

There being no further business to come before the Committee, a motion to adjourn the meeting was made, seconded and so voted and the meeting was declared adjourned.

A true and accurate record.
Attest:
Harlan W. Waksal

PROMISSORY NOTE

Amount: $282,200 Dated: as of December 21, 2000

FOR VALUE RECEIVED, Samuel D. Waksal of 150 Thompson Street, New York, New York ("Maker") promises to pay to ImClone Systems Incorporated of 180 Varick Street, New York, New York 10014, the sum of $282,200, payable upon the earlier of: (i) on demand, or (ii) six months from the date hereof.

Rate of interest on the unpaid principal amount shall be at the prime rate at Citibank, N.A. plus 1%, on the date hereof, to be compounded quarterly.

The Maker of this Note shall have the right to prepay the principal sum at any time without premium or penalty.

The Maker acknowledges that this Note is full-recourse.

The Maker hereby waives presentment, demand for payment, protest, notice of protest, notice of dishonor, and any and all other notices or demands in connection of this Note.

In the event of default, the Maker agrees to pay the cost of collection, including, without limitation, reasonable attorneys' fees and disbursements.

This note shall be governed by and construed in accordance with the laws of the State of New York. The parties agree that jurisdiction for any action, suit or proceeding on this Note shall be in the courts of the United States of America or the State of New York sitting in the Borough of Manhattan in the City of New York, and the Maker hereby irrevocably and unconditionally agrees to submit to the jurisdiction of such courts for purposes of any such action, suit or proceeding.

Samuel D. Waksal, Maker

Witness

waksal\prom397

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Samuel D. Waksal, Maker

Witness

waksal\prom397

ImClone Systems
Incorporated

180 Varick Street
New York, NY 10014
Tel (212) 645-1405
Fax (212) 645-2054
www.imclone.com

MEMORANDUM

TO: Sam Waksal

FROM: Catherine M. Vaczy

DATE: March 2, 2001

SUBJECT: Promissory Note

Attached is the promissory note approved by the executive committee. Please sign and return to the Legal Department. Thanks.

cc: John B. Landes

ImClone Systems Incorporated

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of the Board of Directors

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Samuel D. Waksal, Maker

Witness

waksal\prom397

Received: 2/23/01 4:12PM;
FEB-23-01 15:03 FROM:UTMDACC PRES -> IMCLONE; Page 1
ID: PAGE 1.

FAX

13

The University of Texas
M. D. Anderson Cancer Center
1515 Holcombe Blvd.
Houston, Texas 77030

Date 2/23

Number of pages including cover sheet 17

To:
Catherine Vaczy

Phone:
Fax: 212/645-2770

From:
The Office of the President

- ☐ John Mendelsohn, M.D.
- ☐ Judy Watson
- ☐ Kay Biescar
- ☐ Micha Gregory
- ☒ JoAnne Hale for
- ☐ Jennifer Hubbs
- ☐ Rosemary Quiroz
- ☐ Jennifer Sanders
- ☐ Ann Sharp

Phone: 713-792-6000
Fax: 713-799-2210

REMARKS:

☐ Urgent ☐ For your review ☐ Reply ASAP ☐ Please comment

Hard Copy Follows: X yes ____ no

Received: 2/23/01 4:12PM;
FEB-23-01 15:03 FROM:UTMDACC PRES -> ImCLONE; Page 2
ID:
PAGE 2/1

DIRECTOR QUESTIONNAIRE

INSTRUCTIONS

The following questions seek information necessary to complete the fiscal year 2000 Proxy Statement and Form 10-K Annual Report of ImClone Systems Incorporated ("ImClone or the "Company"), as well as information required by the Company's independent accountants. Most of the questions address Securities and Exchange Commission concerns regarding the relationship of a publicly-held corporation to its directors. Other questions, particularly those found under the "Legal Proceedings" section, reflect the Commission's belief that involvement in certain legal proceedings should be disclosed as such involvement may be material to an evaluation of the ability or integrity of a director.

The Questionnaire is set up with two columns. The column on the left poses the question and provides the answer based on Company records or prior questionnaires. It also asks you to check whether there is "no change" to this information or whether you need to "modify" the information. If you need to "modify" this information, please check "modify" and indicate in what way the information needs modification in the column on the right.

Please complete, sign and return this Questionnaire to Catherine M. Vaczy, Esq., Associate General Counsel, 180 Varick Street, New York, New York 10014 no later than **February 26, 2001**. You may return it by fax if you wish to: (212) 645-2770.

QUESTIONS

(1) Background Information. (a) Please state your full name John Mendelsohn (b) Please indicate your date of birth August 31, 1936	
Questions and responses from Company records or prior Questionnaires. Check either "No change" or "Modify".	**If "Modify", please use this column to provide details as appropriate:**
(c) Please disclose whether you are related by blood, marriage, or adoption, not more remote than first cousin, to any director, executive officer,[1] nominee to become a director or executive officer of the Company, its parent, any subsidiary or other affiliate of the Company. The disclosure, if any, should state (for each relationship) the identity and position of such person and the nature of the relationship Answer: *No* No change ✓ Modify ___	
(c) Please state if you presently hold, or have held, any positions or offices with the company, its parent or any subsidiary or other affiliate of the Company. Answer: ***Director and Consultant*** No Change ✓ Modify ___	

(d) Please state whether you have been selected to serve in your present or expected capacity with the Company pursuant to any arrangement or understanding between yourself and any other person or persons (other than directors or officers of the Company acting solely in their capacities as such). The disclosure, if any, should describe the arrangement or understanding and include the name(s) of such person(s). Answer: *No* No change ✓ Modify ___	
(e) Please disclose your business experience during the past five years (together with applicable dates). The disclosure should include your principal occupations and employment during that period and the name and principal business of any corporation or other organization in which you carried on such occupations and employment. The disclosure also should include all directorships you hold in publicly-traded corporations. Directorships in privately-held corporations, may, but need not be included. ***Note: See biography as it appears at the right. Please indicate any modifications you would like to make.***	**John Mendelsohn, M.D.** has been a Director of the Company since February 1998. He has served as the President of M.D. Anderson Cancer Center, University of Texas, where he has also been Professor of Medicine since 1996. From 1985 to 1996 he was Chairman of the Department of Medicine at Sloan Kettering, New York, as well as holder of the Winthrop Rockefeller Chair in Medical Oncology at Sloan Kettering. He was also Professor and Vice-Chairman of Medicine at Cornell University Medical College and an attending physician at both Memorial and New York Hospitals. Dr. Mendelsohn served on the faculty of the University of California, San Diego and was instrumental in the creation of the University's Cancer Center, where he served as Director from 1976 to 1985. Dr. Mendelsohn's work has focused on growth factors and their role in regulating the proliferation of cancer cells through cell surface receptors. Dr. Mendelsohn was responsible for developing specific monoclonal antibodies that block receptors,

	including epidermal growth factor receptors, which mediate growth factor activation of cell and growth and division. Dr. Mendelsohn is currently a board member of Enron Corp., the Richard Lounsbery Foundation and the Greater Houston Partnership, and a fellow of the New York Academy of Medicine. In 1997, Dr. Mendelsohn was elected to the Institute of Medicine of the National Academy of Sciences.
(f) Please state whether there are any committees of the Company's Board of Directors on which you serve. Answer: ***Member of the Nominating & Corporate Governance Committee and the Research Oversight Committee*** No change ✓ Modify ___	
2. Material Relationships and Transactions. (a) Please state whether there have been any transactions, or series of similar transactions, since January 1, 2000, or any currently proposed transaction, or series of similar transactions, to which the Company or any of its subsidiaries was or is to be a party, in which the amount involved exceeds $60,000 and in which you, any associate[2] of yours or member of your immediate family[3] had, or will have, a direct or indirect material[4] interest. Answer: *No* No change ✓ Modify ___	

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(b) Please state whether you have been at any time since January 1, 2000, an executive officer, director or employee of, or owned of record or beneficially in excess of 10 percent of the equity interest in, any firm, corporation or other business or professional entity: (i) which has made since January 1, 2000, payments to the Company or any of its subsidiaries for property or services in excess of $200,000 or proposes to make such payments. Answer: *No* No change ✓ Modify ___	
(ii) to which the Company or its subsidiaries has made since January 1, 2000, payments for property or services in excess of $200,000 or proposes to make such payments. Answer: ***No, except for any payments relating to clinical trials conducted at MD Anderson.*** No change ✓ Modify ___	
(iii) to which the Company or any of its subsidiaries was indebted at any time since January 1, 2000 in an aggregate amount in excess of $3,000,000. Answer: *No* No change ✓ Modify ___	

(c) Please state whether you have been at any time since January 1, 2000: (i) a member of, or of counsel to, a law firm that the Company retained since January 1, 2000.[6] Answer: *No* No change ✓ Modify ___	
(ii) a partner or executive officer of any investment banking firm that has performed services for the Company or any of its subsidiaries, other than as a participating underwriter in a syndicate, since January 1, 2000.[7] Answer: *No* No change ✓ Modify ___	
(d) Please state whether you have had any relationship with the Company or its management (other than your position as a director or officer) which is substantially similar in nature and scope to those relationships listed in b. and c. above. Answer: *No* No change ✓ Modify ___	
(e) Do you or any members of your immediate family have any interest, direct or indirect, in KPMG LLP?	

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Answer: *No* No change ✓ Modify ___	
3. Legal Proceedings. (a) Please state whether, during the past five years, including any events occurring longer than five years ago if any development relating to such event has occurred during the past five years, (i) any petition under the Federal bankruptcy laws or any State insolvency law has been filed by or against you, or any receiver, fiscal agent or similar officer been appointed by a court for the business or property of you, any partnership in which you were a general partner at or within two years before such filing, or any corporation or business association of which you were an executive officer at or within two years before such filing. Answer: *No* No change ✓ Modify ___	
(ii) you have been convicted in a criminal proceeding, or have been named a subject of a criminal proceeding which is presently pending (excluding traffic violations and other minor offenses). Answer: *No* No change ✓ Modify ___	
(iii) you have been the subject of any court order, judgment or decree, not subsequently reversed, suspended or vacated, which permanently or temporarily enjoined, or otherwise limited, you from any of the following activities:	

(A) acting as a futures commission merchant, introducing broker, commodity trading adviser, commodity pool operator, floor broker, leverage transaction merchant, any other person regulated by the Commodity Futures Trading Commission, or an associated person[2] of any of the foregoing, or as an investment adviser, underwriter, broker or dealer in securities, or as an affiliated person, director or employee of any investment company, bank, savings and loan association or insurance company, or engaging in or continuing any conduct or practice in connection with such activities. Answer: *No* No change ✓ Modify ___	
(B) engaging in any type of business practice. Answer: *No* No change ✓ Modify ___	
(C) engaging in any activity in connection with the purchase or sale of any security or commodity or in connection with any violation of Federal or State securities laws or Federal commodities laws. Answer: *No* No change ✓ Modify ___	

(iv) you have been the subject of any order, judgment or decree, not subsequently reversed, suspended or vacated, of any Federal or State authority barring, suspending or otherwise limiting for more than 60 days your right to engage in any of the activities described in (A) above or your right to be associated with persons engaged in any of such activities. Answer: *No* ✓ No change ____ Modify ___	
(v) you have been found by a court in a civil action or by the Securities and Exchange Commission to have violated any Federal or State securities law, where such judgment or finding has not subsequently been reversed, suspended or vacated, or are presently the subject of any investigation by the Securities and Exchange Commission which could result in the finding of such a violation. Answer: *No* ✓ No change ____ Modify ___	
(vi) you have been found by a court in a civil action or by the Commodities Futures Trading Commission to have violated any Federal commodities law, where such judgment or finding has not been subsequently reversed, suspended or vacated, or are presently the subject of any investigation by the Commodities Futures Trading Commission which could result in the finding of such a violation. Answer: *No* ✓ No change ____ Modify ___	
(vii) you know of any pending or contemplated legal proceedings, including administrative	

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proceedings and investigations by governmental authorities, in which you, any associate[2] of yours, or any affiliate of the Company is or may be a party adverse to the Company, or any subsidiary or in which either you, any associate of yours, or any affiliate of the Company has or may have a material interest adverse to the Company or any subsidiary. Answer: *No* No change ✓ Modify ___	
4. Ownership. (a) Please state whether there are any equity securities of the Company of which you were the beneficial owner[f0] on December 31, 2000. The disclosure, if any, should indicate the amount of equity securities which you own beneficially, which you have a right to acquire within 60 days after December 31, 2000, and as to which you have sole voting power, shared voting power, sole investment power or shared investment power.[11] Answer: ***Please see information at right*** No change ✓ Modify ___	***Directors & Officers - Beneficial Ownership as of December 31, 2000:*** ***For: John Mendelsohn*** ***Shares of Common Stock: 0*** ***Vested Options and Warrants: 410,452; additional 42,500 vesting within 60 days after December 31, 2000.***
(b) Please state whether you wish to disclaim beneficial ownership of any of the shares referenced in 4(a) above. Answer: *No* No change ✓ Modify ___	

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(c) Please state whether there are any persons, including any group of persons,[12] known by you to own beneficially more than 5% of the Company's common stock (or other class of voting securities). Answer: ***None other than as disclosed in public filings.*** No change ✓ Modify ___	
(d) Please state whether you know of any arrangements,[13] including any pledge by any person of securities of the Company or any of its parents, the operation of which may at a subsequent date result in a change in control[9] of the Company. This disclosure does not require a description of ordinary default provisions contained in the Company's charter, trust indentures or other governing instruments relating to securities of the Company. Answer: *No* No change ✓ Modify ___	
(e) Please state whether you know of any voting trust or similar agreement or arrangement[13] under which more than 5% of the Company's outstanding voting securities is held or is to be held. The disclosure, if any, should describe, in each case, the amount held or to be held pursuant to the trust or agreement, its duration, the names and addresses of the voting trustees, and their voting rights and other powers under the trust or agreement.	

Answer: *No* No change ✓ Modify ___	
(f) Please confirm that you have advised the Company of any and all acquisitions and dispositions made by you during 2000 (excluding option or warrant exercises) of the Company's securities so that a Form 4 could be filed with the SEC on your behalf. Yes *X* No ___	

CONCLUDING STATEMENT

I understand that this information is furnished to you for use in connection with the preparation of registration statements under the Securities Act or the Securities Exchange Act, proxy statements on Schedule 14A and annual reports on Form 10-K.

I will promptly notify you of any changes in such information which may occur subsequent hereto and prior to March 15, 2001. I understand and agree that this Questionnaire, as completed by me, and my further communications regarding the matters contemplated herein, will be relied upon by you, the Company, the representatives of the underwriters and their respective counsel in connection with the preparation of the above-referenced documentation.

I understand that material misstatements or the omission of material facts in the above-referenced documentation may give rise to civil and criminal liabilities to the Company and to each officer and director of the Company signing such documentation and other persons signing such documentation. I will notify you and the Company of any such misstatement of a material fact or any amendment thereto, and of the omission of any material fact necessary to make the statements contained therein not misleading, as soon as practicable after a copy of any such document or any such amendment thereto has been provided to me.

I confirm that the foregoing statements are correct, to the best of my knowledge and belief.

Signature

John Mendelsohn
Director

Date: 2/23, 2001

/SEC/PROXY2000/mendelsohn.director.questionnaire

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Footnotes

1. The term "**executive officer**" means the president, secretary, treasurer, any vice-president in charge of a principal business function (such as sales, administration, or finance) and any other person who performs similar policy-making functions for the Company. Executive officers of subsidiaries may be deemed executive officers of the Company if they perform such policy making functions for the Company.

2. The term "**associate**" means any corporation or organization (other than the Company or any of its subsidiaries) of which you are an officer or partner or are, directly or indirectly, the beneficial owner of 10% or more of any class of equity securities, any trust or other estate in which you have a beneficial interest or as to which you serve as trustee or in a similar capacity, and your spouse, or any relative of yours or relative of your spouse living in your home or who is a director or officer of the Company or of any of its parents (if any) or subsidiaries. Please identify the associate referred to in your answer and indicate such person's relationship with you or the Company.

3. The "**immediate family**" of a person includes such person's spouse, parents, children, siblings, mothers and fathers-in-law, sons and daughters-in-law, and brothers and sisters-in-law.

4. The term "**material**", when used in this Questionnaire to describe a requirement for the furnishing of information as to any subject, refers to information relating to matters about which an average investor might reasonably wish or expect to be informed before determining whether to buy or sell securities of the Company.

5. In describing any transaction involving the purchase or sale of assets by or to the Company or any of its subsidiaries, otherwise than in the ordinary course of business, disclose the cost of the assets to the purchaser and, if acquired by the seller within two years prior to the transaction, the cost thereof to the seller. Disclose the principle followed in determining the Company's purchase or sale price and the name of the person making such determination.

   In computing the amount involved in the transaction or series of similar transactions, disclose all periodic installments in the case of any lease or other agreement providing for periodic payments or installments. The

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amount of your interest should be computed without regard to the amount of profit or loss involved in the transaction(s).

6. If the dollar amount of fees paid or expected to be paid to a law firm exceeds five percent of the law firm's gross revenues for that firm's last full fiscal year, then disclose the amount of such fees.

7. If the dollar amount of compensation received by an investment banking firm exceeds five percent of the investment banking firm's consolidated gross revenues for that firm's last full fiscal year, then disclose the amount of such compensation.

8. The term "**promoter**" means any person who, acting alone or in concert with one or more persons, directly or indirectly takes initiative in founding and organizing the business or enterprise of a company. The term includes any person who, in connection with the founding and organizing of the business or enterprise of a company, directly or indirectly receives in consideration of services or property (or both) 10% or more of any class of securities of the company or 10% or more of the proceeds from the sale of any class of securities. However, a person who receives such securities or proceeds either solely as underwriting commissions or solely in consideration of property shall not be deemed a "promoter" if such person does not otherwise take part in founding and organizing the enterprise.

9. The term "**control**" means the possession, direct or indirect, of the power to direct or cause the direction of the management and policies of the Company, whether through the ownership of voting securities, by contract, or otherwise.

10. You are the "**beneficial owner**" of a security if you directly or indirectly, through any contract, arrangement, understanding, relationship, or otherwise, have or share: (i) voting power which includes the power to vote, or to direct the voting of, such security, or (ii) investment power which includes the power to dispose, or to direct the disposition of, such security. You are deemed the beneficial owner of a security if you, directly or indirectly, create or use a trust, proxy, power of attorney, pooling arrangement or any other contract, arrangement, or device with the purpose or effect of divesting yourself of beneficial ownership of a security or preventing the vesting of such beneficial ownership. Finally, you are deemed to be the beneficial owner of a security if you have the right to acquire beneficial ownership of such security at any time within sixty days, including but not limited to any right to acquire (a) through the exercise of any option, warrant or right, or (b) through the conversion of a

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security, or (c) pursuant to the power to revoke a trust, discretionary account, or similar arrangement, or (d) pursuant to the automatic termination of a trust, discretionary account or similar arrangement. If you have acquired any security or power specified in (a), (b) or (c) above, with the purpose or effect of changing or influencing the control of the issuer, or in connection with or as a participant in any transaction having such purpose or effect, then immediately upon such acquisition you are deemed to be the beneficial owner of the securities which may be acquired through the exercise or conversion of such security or power.

All securities of the same class that are beneficially owned by you, regardless of the form which such beneficial ownership takes, must be aggregated in calculating the number of shares beneficially owned by you.

The above definition is broad and although you may not actually have or share voting or investment power with respect to securities owned by persons in your family or living in your home, you should include such shares in your beneficial ownership disclosure, and then, as appropriate, disclaim beneficial ownership of such securities. If you disclaim, please furnish the information described in Part 4(b)

11. Disclose separate information with respect to different classes of securities held and whether securities held are those of the Company or of a parent or subsidiary of the Company.

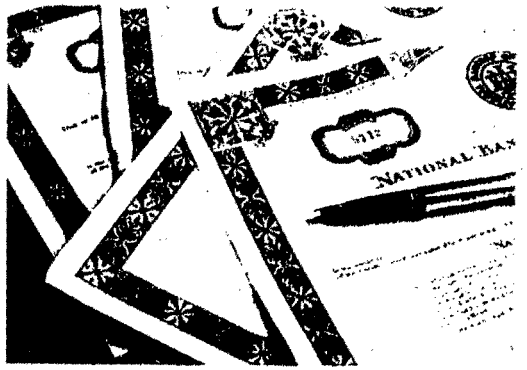
12. In addition to disclosing with respect to any individual, please disclose with respect to any "group" as that term is used in Section 13d-3 of the Exchange Act. Section 13d-3 states that "when two or more persons act as a partnership, limited partnership, syndicate, or other group for the purpose of acquiring, holding, or disposing of securities of an issuer, such syndicate or *group* shall be deemed a person for the purposes of this subsection" (emphasis added).

13. The term "**arrangement**" means any plan, contract, authorization or understanding, whether or not set forth in a formal document.

KPMG

Confidential Treatment Requested by ImClone Systems, Inc.

ImClone Systems Incorporated



Report to the Audit Committee of the Board of Directors

March 28, 2001

This report is intended solely for the information and use of the Audit Committee and management and is not intended to be and should not be used by anyone other than these specified parties.

ASSURANCE

HCEC 28465

392

Agenda

- Results of 2000 Audit
- Significant Audit Matters
- Required Audit Committee Communications ("SAS 61")
- Independence Letter

KPMG

ASSURANCE

1010SHGR

Results of 2000 Audit

- Audit substantially complete
- Expect to issue an unqualified opinion
- No significant audit differences

KPMG

Confidential Treatment Requested by Imclone Systems, Inc.

HCEC 28467

ASSURANCE

KPMG

Significant Audit Matters

Adoption of Staff Accounting Bulletin No. 101 in the fourth Quarter of 2000

- Cumulative effect adjustment - $2.6 million
- Represents the upfront payments received on the BEC2 development and commercialization agreement
- Establishment of deferred revenue to be amortized to earnings over the patent life
- Restatement of quarterly results

Equity Transactions

- Conversion of 100,000 shares of Preferred Stock
- Redemption of 200,000 shares of Preferred Stock
- Options granted to consultants – $4.4 million charge

KPMG

Significant Audit Matters, Cont.

Merck IMC-C225 Agreement

- Receipt of an additional $8 million in milestone payments during 2000. Total deferred as of December 31, 2000 is $28 million.
- Reimbursement of 50% of Radiotherapy Trial Study 9815 costs - $2.6 million
- In March 2001, ImClone received an irrevocable waiver from Merck that will allow the milestone revenue currently deferred to be recognized in the first quarter of 2001.

Convertible Note Offering

- In February 2000, ImClone completed a private placement of $240 million convertible subordinated notes.
- In connection with the offering, ImClone recognized deferred financing costs of $8.5 million which are being amortized into interest expense over the life of the debt (60 months).

Investment in ValiGen

- Aggregate purchase price of $7.5 million
- Write-down of approximately $5 million based on the modified equity method recognized during the fourth quarter.

KPMG

Significant Audit Matters, Cont.

Lonza development and manufacturing services agreement

- $5.4 million recognized in 2000 research and development expense
- Purchase commitment

Construction in Progress

- $32 million increase in CIP from prior year. Principally relates to the construction of the Branchburg manufacturing facility.

Clinical Trial Accruals

KPMG

SAS 61 Required Communications

Responsibilities Under Generally Accepted Auditing Standards (GAAS)	■ Conduct our audit in accordance with GAAS which provides reasonable - not absolute - assurance about whether the financial statements are free of material misstatement, whether caused by error or fraud ■ No responsibility to obtain reasonable assurance that misstatements that are not material are detected
Scope of Audit	■ No significant changes to planned audit scope
Report on Audit	■ Unqualified opinion, with reference to accounting change

KPMG

SAS 61 Required Communications, Cont.

Internal Controls

- Considered internal controls to extent necessary to determine our auditing procedures for the purpose of expressing our opinion on the financial statements
- An audit does not provided assurance on the internal control system
- No material weaknesses noted
- Payment of bonus to CEO

Other Information in Documents Containing Audited Financial Statements

- Annual Report
- Form 10-K

- No matters came to our attention that cause us to believe such information is materially inconsistent with the consolidated financial statements
- Our responsibility is to financial information identified in our auditors' report

KPMG

SAS 61 Required Communications, Cont.

Management Judgments and Accounting Estimates

- ValiGen investment
- Fair value of stock-based compensation
- Clinical trial accruals

We evaluated management's judgments and accounting estimates in determining whether related accounts are reasonable in relation to the consolidated financial statements taken as a whole.

KPMG

SAS 61 Required Communications, Cont.

Significant Accounting Policies / Quality of Accounting Principles	■ The significant accounting policies used by the Company are described in Note 2 to the consolidated financial statements
	■ Recognition of nonrefundable milestone revenues upon achievement
	■ Deferral and amortization of up-front nonrefundable license fees in accordance with SAB No. 101
	■ Costs to produce commercial lots of inventory are expensed prior to regulatory approval
Significant Audit Adjustments	■ None
Difficulties Encountered With Management in Performing the Audit	■ None

KPMG

SAS 61 Required Communications, Cont.

Major Issues discussed with Management Prior to Retention	■ None
Disagreements With Management	■ None
Consultation with Other Accountants	■ Not aware of any
Other Matters	■ No Management Advisory Services were rendered during 2000

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FILED AS OF DATE: 20010423

FILER:

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CENTRAL INDEX KEY: 0000765258
STANDARD INDUSTRIAL CLASSIFICATION: BIOLOGICAL PRODUCTS (NO DIAG
IRS NUMBER: 042834797
STATE OF INCORPORATION: DE
FISCAL YEAR END: 1231

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SEC ACT:
SEC FILE NUMBER: 000-19612
FILM NUMBER: 1608767

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CITY: NEW YORK
STATE: NY
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PROXY STATEMENT PURSUANT TO SECTION 14(a) OF THE SECURITIES
EXCHANGE ACT OF 1934 (AMENDMENT NO.)

Filed by the Registrant [X]

Filed by a Party other than the Registrant [ ]

Check the appropriate box:

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[ ] Preliminary Proxy Statement
[ ] Confidential, for Use of the Commission Only (as permitted by Rule 14a-6(e)(2))
[X] Definitive Proxy Statement
[ ] Definitive Additional Materials
[ ] Soliciting Material Pursuant to sec.240.14a-11(c) or sec.240.14a-12
</TABLE>

IMCLONE SYSTEMS INCORPORATED

(Name of Registrant as Specified In Its Charter)

(Name of Person(s) Filing Proxy Statement, if other than the Registrant)

Payment of Filing Fee (Check the appropriate box):

[X] No fee Required.

[ ] Fee computed on table below per Exchange Act Rules 14a-6(i)(4) and 0-11.

(1) Title of each class of securities to which transaction applies:

---

(2) Aggregate number of securities to which transaction applies:

---

(3) Per unit price or other underlying value of transaction computed pursuant to Exchange Act Rule 0-11 (Set forth the amount on which the filing fee is calculated and state how it was determined):

---

(4) Proposed maximum aggregate value of transaction:

---

(5) Total fee paid:

[ ] Fee paid previously with preliminary materials.

[ ] Check box if any part of the fee is offset as provided by Exchange Act Rule 0-11(a)(2) and identify the filing for which the offsetting fee was paid previously. Identify the previous filing by registration statement number, or the Form or Schedule and the date of its filing.

(1) Amount Previously Paid:

---

(2) Form, Schedule or Registration Statement No.:

---

(3) Filing Party:

---

(4) Date Filed:

<PAGE> 2

[IMCLONE LOGO]

IMCLONE SYSTEMS INCORPORATED
180 Varick Street
New York, NY 10014
(212) 645-1405

NOTICE OF ANNUAL MEETING OF STOCKHOLDERS

DATE: May 24, 2001
TIME: 10:00 A.M. (Local Time)
PLACE: Le Parker Meridien Hotel New York
118 West 57th Street
New York, New York 10019

ITEMS OF BUSINESS:

1. Election of ten directors.

2. Ratification of the appointment of KPMG LLP as the Company's independent certified public accountants for the fiscal year ending December 31, 2001.

3. Any other matters properly brought before the shareholders at the meeting.

RECORD DATE:

Only holders of the common stock of record at the close of business on April 9, 2001 are entitled to notice of and to vote at the meeting.

ANNUAL REPORT:

Our 2000 Annual Report, which is not a part of the proxy soliciting material, is enclosed.

PROXY VOTING:

It is important that your shares be represented and voted at the meeting. To vote, please complete, sign and date the enclosed proxy and promptly return it in the envelope provided. Sending in your proxy will not prevent you from voting in person at the meeting.

By Order of the Board of Directors

/s/ John B. Landes

John B. Landes
Secretary

New York, New York
April 23, 2001
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IMCLONE SYSTEMS INCORPORATED
180 VARICK STREET
NEW YORK, NEW YORK 10014

PROXY STATEMENT

This proxy statement is furnished in connection with the solicitation of proxies for use at the Annual Meeting of Stockholders of ImClone Systems Incorporated (the "Company") to be held at 10:00 a.m., local time, on Thursday, May 24, 2001, at Le Parker Meridian Hotel, 118 West 57th Street, New York, New York 10019, and at any adjournments thereof. The Notice of Annual Meeting, this proxy statement and the accompanying proxy card are first being mailed to stockholders on or about April 24, 2001.

ABOUT THE MEETING

What is the purpose of the meeting?

At the meeting, stockholders will act upon the matters outlined in the accompanying notice of meeting, including the election of Directors and ratification of the Company's independent auditors. In addition, the Company's management will report on the performance of the Company during fiscal 2000 and respond to questions from stockholders.

Who is entitled to vote?

Only stockholders of record at the close of business on the record date, April 9, 2001, are entitled to receive notice of the meeting and to vote the shares of common stock that they held on that date at the meeting, or any postponement or adjournment of the meeting. Each outstanding share entitles its holder to cast one vote on each matter to be voted upon.

Who may attend the meeting?

Although we encourage you to complete and return the proxy card to ensure that your vote is counted, you can attend the annual meeting and vote your shares in person. All stockholders as of the record date, or their duly appointed proxies, may attend the meeting. To ensure the availability of adequate space for ImClone Systems stockholders wishing to attend the meeting, priority seating will be given to stockholders of record, stockholders who hold their shares in "street name" (that is, through a broker or other nominee) and invited guests of management. In addition, a stockholder may bring one guest. In order that seating may be equitably allocated, a stockholder wishing to bring more than one guest must write to the Corporate Secretary of the Company in advance of the meeting and receive written concurrence.

What constitutes a quorum?

The presence at the meeting, in person or by proxy, of the holders of a majority of the shares of common stock outstanding on the record date will constitute a quorum, permitting the meeting to conduct its business. As of the record date, 66,520,491 shares of common stock of the Company were outstanding. Proxies received but marked as abstentions and broker non-votes will be included in the calculation of the number of shares considered to be present at the meeting.

How do I vote?

If you complete and properly sign the accompanying proxy card and return it to the Company, it will be voted as you direct. If you are a registered stockholder and attend the meeting, you may deliver your completed proxy card in person. "Street name" stockholders who wish to vote at the meeting will need to obtain a proxy form from the institution that holds their shares.

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Can I change my vote after I return my proxy card?

Yes. Even after you have submitted your proxy, you may change your vote at any time before the proxy is exercised by filing with the Secretary of the Company either a notice of revocation or a duly executed proxy bearing a later date. The powers of the proxy holders will be suspended if you attend the meeting in person and so request, although attendance at the meeting will not by itself revoke a previously granted proxy.

What are the Board's recommendations?

The persons named as proxy holders on the proxy card will vote in accordance with the recommendations of the Board of Directors (the "Board"). The Board's recommendation is "for" each of the items set forth in this proxy statement. With respect to any other matter that properly comes before the meeting, the proxy holders will vote as recommended by the Board or, if no recommendation is given, in their own discretion.

What vote is required to approve each item?

Election of Directors. The affirmative vote of a plurality of the votes cast at the meeting is required for the election of directors.

Other Items. For each other item, the affirmative vote of the holders of a majority of the shares present in person or represented by proxy and entitled to vote on the item will be required for approval. A properly executed proxy marked "ABSTAIN" with respect to any such item will not be voted although it will be counted for purposes of determining the number of votes cast on the item. Accordingly, an abstention will have the effect of a negative vote. An abstention will, however, be counted for purposes of determining whether there is quorum.

How are votes counted?

If you hold your shares in "street name" through a broker or other nominee, your broker or nominee will be able to vote your shares without instruction from you on matters that the New York Stock Exchange determines to be routine and will not be permitted to vote your shares on matters that the New York Stock Exchange does not determine to be routine. Thus, if you do not give your broker or nominee specific instruction on non-routine matters, your shares may not be voted on those matters and will not be counted in determining the number of shares necessary for approval on those matters. Shares represented by such "broker non-votes" will, however be counted in determining whether there is a quorum and in determining the number of votes cast on a routine item.

Who pays for this proxy solicitation?

We do. In addition to sending you these materials, some of our employees may contact you by telephone, by mail, or in person. None of these employees will receive any extra compensation for doing this. In addition, we have retained Corporate Investor Communications, Inc. to assist us in soliciting your proxy for a fee of $5,000 plus reasonable out-of-pocket expenses.

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STOCK OWNERSHIP

Who are the Largest Owners of the Company's Stock?

Except as set forth in the table below, the Company knows of no single person or group of related persons that is the beneficial owner of more than 5% of the Company's common stock. This is based solely on Schedule 13G and Schedule 13D reports filed with the Securities and Exchange Commission ("SEC") as of March 28, 2001.

How Much Stock Do Certain Beneficial Owners, the Company's Directors and Certain Officers Own?

The following table shows the amount of common stock of the Company beneficially owned (unless otherwise indicated) by persons or groups of related persons that beneficially own greater than 5% of the Company's common stock, the Company's directors, the Named Officers in the Summary Compensation Table below and the directors and executive officers of the Company as a group. Except as otherwise indicated, all information is as of March 28, 2001. "Beneficial Ownership" is a technical term defined by the SEC to mean more than ownership in the usual sense. For example, you "beneficially own" our common stock if you own it directly or indirectly (e.g., through a relationship, a position as a director or trustee or through an agreement). The table below, as well as all other portions of this proxy statement, give effect to the Company's 2-for-1 stock split, effected in the form of a dividend, in October 2000.

<TABLE>
<CAPTION>

BENEFICIAL OWNER(1)	BENEFICIALLY OWNED	BENE OW
<S>	<C>	<C>
FMR Group 82 Devonshire Street Boston, Massachusetts 02109	9,820,438(3)	
Samuel D. Waksal, Ph.D.	4,506,733(4)	
Harlan W. Waksal, M.D.	3,618,560(5)	
Robert F. Goldhammer	1,641,552(6)	
John B. Landes	510,500(7)	
John Mendelsohn, M.D.	452,952(8)	
David M. Kies	400,015(9)	
Vincent T. DeVita, Jr., M.D.	206,684(10)	
Paul B. Kopperl	191,420(11)	
William R. Miller	138,094(12)	
Richard Barth	135,000(13)	
Ronald A. Martell	84,640(14)	
S. Joseph Tarnowski, Ph.D.	54,648(15)	
Arnold J. Levine	49,974(16)	
All directors and executive officers as a group (10 persons)(17)	11,340,984(17)	

</TABLE>

* Less than 1%.

(1) Unless otherwise noted, each person's address is in care of ImClone Systems Incorporated, 180 Varick Street, Sixth Floor, New York, New York 10014.

(2) The percentage of voting stock owned by each stockholder is calculated by dividing (i) the number of shares deemed to be beneficially held by such stockholder as of March 28, 2001, as determined in accordance with Rule

13d-3 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), by (2) the sum of (A) 66,489,780, which is the number of shares of common stock outstanding as of March 28, 2001 plus (B) the number of shares of common stock issuable upon exercise of currently exercisable options and warrants held by such stockholder. For purposes of this security ownership table "currently exercisable options" and "currently exercisable warrants" consist of options and warrants exercisable as of March 28, 2001 or within 60 days after March 28, 2001.

(3) This information is as of December 31, 2000 and was obtained from a Schedule 13G amendment filed with the SEC on February 14, 2001. It includes a total of 232,345 shares of common stock issuable upon conversion of $12,800,000 principal amount of ImClone Systems Incorporated 5 1/2% convertible notes due 2005. FMR Group is the parent company of various Fidelity funds and related parties.

(4) Includes 2,060,000 shares issuable upon the exercise of currently exercisable options.

(5) Includes 2,080,000 shares issuable upon the exercise of currently exercisable options and 5,200 shares owned by Dr. Waksal's sons.

(6) Includes 352,084 shares issuable upon the exercise of currently exercisable options; 620,600 shares issuable upon the exercise of currently exercisable warrants; and 15,000 shares held by Mr. Goldhammer's spouse.

(7) Includes 290,000 shares issuable upon exercise of currently exercisable options.

(8) Consists of 452,952 shares issuable upon the exercise of currently exercisable options.

(9) Includes 115,000 shares issuable upon the exercise of currently exercisable options, 16,400 shares held by Mr. Kies as custodian for his minor son and 615 shares held by Mr. Kies' spouse as to which Mr. Kies disclaims beneficial ownership.

(10) Includes 206,084 shares issuable upon the exercise of currently exercisable options.

(11) Includes 150,000 shares issuable upon the exercise of currently exercisable options and 500 shares held by Mr. Kopperl's spouse as to which Mr. Kopperl disclaims beneficial ownership.

(12) Includes 42,500 shares issuable upon exercise of currently exercisable options.

(13) Consists of 135,000 shares issuable upon exercise of currently exercisable options.

(14) Includes 82,500 shares issuable upon exercise of currently exercisable options.

(15) Includes 53,500 shares issuable upon exercise of currently exercisable options.

(16) Consists of 49,974 shares issuable upon exercise of currently exercisable

options and warrants.

(17) Includes an aggregate of (1) 6,264,194 shares issuable upon the exercise of currently exercisable options and warrants and (2) 1,115 shares as to which beneficial ownership is disclaimed. Notwithstanding that Mr. Martell, Dr. Tarnowski and Mr. Landes are included in the Summary Compensation Table included in this proxy statement, shares held by Mr. Martell, Dr. Tarnowski and Mr. Landes have not been included as they are not considered to be executive officers of ImClone Systems.

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PROPOSAL NO. 1

ELECTION OF BOARD OF DIRECTORS

An entire Board of Directors, consisting of ten members, will be elected at the meeting. The directors elected will hold office until their successors are elected, which should occur at the next annual meeting.

Nominations. At the meeting, the Board of Directors will nominate the persons named in this proxy statement as directors. Although we do not know of any reason why any of these nominees might not be able to serve, the Board of Directors will propose a substitute nominee if any nominee is not available for election.

General Information About the Nominees. All of the nominees are currently directors of the Company. Each of the nominees has agreed to be named in the proxy statement and to serve as a director if elected.

NOMINEES FOR DIRECTOR

<TABLE>
<CAPTION>

NAME	CURRENT POSITION WITH COMPANY	D CO
<S>	<C>	<C
Richard Barth(1)(2).....	Director	
Vincent T. DeVita, Jr., M.D.(5).....	Director	
Robert F. Goldhammer(2)(3)(4).....	Chairman of the Board	
David M. Kies(2)(4).....	Director	
Paul B. Kopperl(1)(2)(4).....	Director	
Arnold J. Levine, Ph.D.....	Director	
John Mendelsohn, M.D.(4)(5).....	Director	
William R. Miller(1)(4).....	Director	
Harlan W. Waksal, M.D.(3)(4)(5).....	Executive Vice President, Chief Operating Officer and Director	
Samuel D. Waksal, Ph.D.(3)(5).....	President, Chief Executive Officer and Director	

</TABLE>

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(1) Member of Audit Committee

(2) Member of Compensation and Stock Option Committee

(3) Member of Executive Committee

(4) Member of Nominating and Corporate Governance Committee

(5) Member of Research Oversight Committee

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BUSINESS EXPERIENCE OF NOMINEES FOR DIRECTOR

RICHARD BARTH, 69, has been a Director of the Company since October 1996. Mr. Barth served as Chairman of the Board of Ciba-Geigy Corporation, United States ("Ciba-Geigy") from 1990 until December 1996, and was President and Chief Executive Officer of Ciba-Geigy from 1986 until April 1996. Mr. Barth is a member of the Board of Directors of numerous organizations, including The Bank of New York, Bowater, Inc. and New York Medical College.

VINCENT T. DEVITA, JR., M.D., 66, has been a Director of the Company since February 1992. Since 1995, Dr. DeVita has served as Director of the Yale Cancer Center as well as Professor of Medicine and Professor of Epidemiology and Public Health at Yale University School of Medicine, New Haven, Connecticut. From September 1988 through June 1995, Dr. DeVita served as Attending Physician at Memorial Sloan Kettering Cancer Center ("Sloan Kettering"), New York, and through June 1991 as Physician-in-Chief. From 1980 to 1988, he served under Presidential appointment as Director of the National Cancer Institute ("NCI"), where he had held various positions since 1966. During his years with the NCI, Dr. DeVita was instrumental in developing the first successful combination cancer chemotherapy program. This work ultimately led to effective regimens of curative chemotherapy for a variety of cancers. Dr. DeVita's numerous awards include the 1990 Armand Hammer Cancer Prize and the 1982 Albert and Mary Lasker Medical Research Award for his contribution to the cure of Hodgkin's disease. Dr. DeVita received his M.D. from the George Washington University School of Medicine, Washington, D.C. in 1961.

ROBERT F. GOLDHAMMER, 70, has served as the Company's Chairman of the Board since February 1991 and has been a Director of the Company since October 1984. Mr. Goldhammer has been a partner of Concord International Group, L.P. since 1991. He was a partner of Rohammer Corporation, a private investment company, from 1989 to 1991. He was a managing director of Kidder, Peabody Group Inc., an investment banking firm, from May 1988 to January 1989. He is a director of Esterline Technologies Corporation.

DAVID M. KIES, 57, has been a Director of the Company since June 1996. Mr. Kies is a Partner of the New York based law firm Sullivan & Cromwell, specializing in mergers and acquisitions, securities and general corporate matters.

PAUL B. KOPPERL, 67, has served as a Director of the Company since December 1993. He is President of Pegasus Investments, Inc., Boston, a private investment management firm established in 1994. He has served as President of Delano & Kopperl, Inc., a private business strategy and venture investing firm in Boston and its predecessor firms from 1976 to the present. From 1967 through 1975, he was Vice President and a principal of Kidder, Peabody & Co. Incorporated, New York an investment banking firm. From 1959 to 1967 he was an associate with Goldman, Sachs & Co., New York. Mr. Kopperl is a Trustee and Governor of the Dana-Farber Cancer Institute, Boston and a member of its Executive, Investment and Trustee Science Committees. He serves as Advisor to the Dean, Harvard School of Public Health. Over the years he has served as a trustee or director of numerous businesses and not-for-profit educational, performing arts and social welfare organizations.

ARNOLD J. LEVINE, PH.D., 60, has served as a member of the Board since April 2000. Dr. Levine is a cancer biologist and is President of Rockefeller University. Previously, Dr. Levine was the Harry C. Wiess Professor of Life Sciences at Princeton University, where he founded Princeton's molecular biology department during a 12-year tenure that saw the department grow to include two research laboratories and 35 faculty members. Prior to his work at Princeton, Dr. Levine was Chairman at SUNY Stony Brook School of Medicine. Dr. Levine is also a Director of PE Corporation, Baxter International, Inc., Genomica Corp. and Advanced Medicine.

JOHN MENDELSOHN, M.D., 64, has been a Director of the Company since February 1998. He has served as the President of M.D. Anderson Cancer Center, University of Texas, where he has also been Professor of Medicine since 1996. From 1985 to 1996 he was Chairman of the Department of Medicine at Sloan Kettering, New York, as well as holder of the Winthrop Rockefeller Chair in Medical Oncology at Sloan Kettering. He was also Professor and Vice-Chairman of Medicine at Cornell University Medical College and an attending physician at both Memorial and New York Hospitals. Dr. Mendelsohn served on the faculty of the University

of California, San Diego and was instrumental in the creation of the University's Cancer Center, where he served as Director from 1976 to 1985. Dr. Mendelsohn's work has focused on growth factors and their role in regulating the proliferation of cancer cells through cell surface receptors. Dr. Mendelsohn was responsible for developing specific monoclonal antibodies that block receptors, including epidermal growth factor receptors, which mediate growth factor activation of cell growth and division. Dr. Mendelsohn is currently a board member of Enron Corp., the Richard Lounsbery Foundation and the Greater Houston Partnership, and a fellow of the New York Academy of Medicine. In 1997, Dr. Mendelsohn was elected to the Institute of Medicine of the National Academy of Sciences.

WILLIAM R. MILLER, 72, has been a Director of the Company since June 1996. Mr. Miller served as Vice Chairman of the Board of Directors of the Bristol-Myers Squibb Company from 1985 until 1991, at which time he retired. Mr. Miller is a director of Isis Pharmaceuticals, Inc. and Transkaryotic Therapies, Inc. He is Chairman of the Board of Vion Pharmaceuticals, Inc. He is Chairman of the Board of Trustees of the Cold Spring Harbor Laboratory and is a past Chairman of the Board of the Pharmaceutical Manufacturers Association. Mr. Miller is a Trustee of the Manhattan School of Music, Metropolitan Opera Association and Opera Orchestra of New York. He is a member of Oxford University Chancellor's Court of Benefactors, Honorary Fellow of St. Edmund Hall and Chairman of the English-Speaking Union of the United States.

HARLAN W. WAKSAL, M.D., 48, is a founder of the Company and has been a Director since April 1984. He has directed the Company's research and development since April 1985, and has served as the Company's Executive Vice President and Chief Operating Officer since March 1987. From 1985 to March 1987, Dr. Waksal served as the Company's President. Dr. Waksal received his training in Internal Medicine from Tufts-New England Medical Center Hospital and in Pathology from Kings County Hospital in Brooklyn, New York from 1982 to 1987. From 1984 to 1985, Dr. Waksal was Chief Resident in Pathology at Kings County Hospital. He received his Medical Degree from Tufts University School of Medicine in 1979. He is currently Adjunct Assistant Professor in the Department of Pathology at Downstate Medical Center, New York. Dr. Harlan Waksal and Dr. Samuel Waksal are brothers.

SAMUEL D. WAKSAL, PH.D., 53, President and Chief Executive Officer of the Company, is a founder of the Company and has been its Chief Executive Officer and a Director since August 1985 and President since March 1987. From 1982 to 1985, Dr. Waksal was a member of the faculty of Mt. Sinai School of Medicine as Associate Professor of Pathology and Director of the Division of Immunotherapy within the Department of Pathology. He has served as visiting Investigator of the National Cancer Institute, Immunology Branch, Research Associate of the Department of Genetics, Stanford University Medical School, Assistant Professor of Pathology at Tufts University School of Medicine and Senior Scientist for the Tufts Cancer Research Center. Dr. Waksal was a scholar of the Leukemia Society of America from 1979 to 1984. Dr. Waksal has been a visiting professor at the Weizmann Institute in Israel and the Pasteur Institute in France. He sits on the Board of Directors of ValiGen. Dr. Waksal currently serves on the Executive Committee of the New York Biotechnology Association, the Board of Advisors of Rockefeller University and is Chairman of the New York Council for the Humanities. Dr. Samuel Waksal and Dr. Harlan Waksal are brothers.

THE BOARD RECOMMENDS A VOTE "FOR" EACH OF THE NOMINEES NAMED ABOVE (PROPOSAL NO. 1 ON YOUR PROXY CARD).

DIRECTORS' COMPENSATION

CASH COMPENSATION

Exclusive of the Chairman, each Director of the Company, who is not a full-time employee of the Company or who does not otherwise provide consulting services to the Company receives compensation of $10,000 per year, or a pro rata portion thereof for persons not serving the full fiscal year, for such person's services as a Director as well as reimbursement of the Director's reasonable out-of-pocket expenses incurred in connection with his Board and Board committee activities. The Chairman, who is not a full-time employee of the Company, receives $150,000 per year for his services as Chairman as well as reimbursement of his reasonable out of pocket expenses incurred in connection with his Board and Board committee activities. In addition, subject to the first sentence of this paragraph, the Chairman of each of the Board committee receives $5,000 per year as compensation for the services of each as Chairman.

DIRECTORS' STOCK OPTIONS

Pursuant to the Company's 1996 Non-Qualified Stock Option Plan (the "1996 Non-Qualified Plan"), Directors who are not full-time employees of the Company automatically receive on each February 15th an option to purchase a specified number of shares of common stock. Individuals joining the Board during the course of the year receive a pro rata portion thereof. This specified number was 15,000 shares for 2000; however, the amount was increased to 30,000 shares in 2001 by vote of the Board due to the 2-for-1 stock split effected by the Company in 2000, except that for the Chairman who is not a full-time employee of the Company for whom this number was increased from 30,000 to 60,000 shares. Such options vest after one full year of service on the Board from the date of grant and have an exercise price equal to the fair market value of the common stock on the date of grant. Directors newly joining the Board who are not full-time employees of the Company are made a one-time option grant under the 1996 Non-Qualified Plan to purchase 50,000 shares of common stock. Such options vest as to 25% of the shares of common stock over the four-year period commencing with the date of grant, subject to such individual's continued service on the Board on the scheduled date of vesting, and have an exercise price equal to the fair market value of the common stock on the date of grant. From time to time,

directors who are not full-time employees of the Company may be granted additional options in consideration for providing services on the Board. No such additional grants were made during 2000.

The table below sets forth option grants to Directors who are not full-time employees of the Company during the year ended December 31, 2000 in consideration for such Directors serving on the Board:

<TABLE>
<CAPTION>

NAME	NUMBER OF OPTIONS
<S>	<C>
Richard Barth	30,000(1)
Vincent T. DeVita, Jr.	30,000(1)
Robert F. Goldhammer	60,000(1)
David M. Kies	30,000(1)
Paul B. Kopperl	30,000(1)
Arnold J. Levine	21,474(2)
	50,000(2)
John Mendelsohn	30,000(1)
William R. Miller	30,000(1)

</TABLE>

(1) These options were granted automatically pursuant to the terms of the 1996 Non-Qualified Plan on February 15, 2000 at a per share exercise price of $38.91 which is equal to the fair market value of the common stock on the date of grant. They vested and became exercisable in their entirety on February 15, 2001 and terminate February 14, 2010.

(2) Dr. Levine joined the Board on April 14, 2000. The option to purchase 21,474 shares was granted to Dr. Levine as a pro rata amount of the automatic option grant to purchase 30,000 shares under the 1996

Non-Qualified Plan due to the fact that he would not be serving the full fiscal year. This option is exercisable at a per share exercise price of $34.50 which is equal to the fair market value of the common stock on the date of grant. It vested in its entirety on April 14, 2001 and terminates on April 13, 2010. The option to purchase 50,000 shares was issued in accordance with Company policy when Dr. Levine joined the Board and is exercisable at a per share exercise price of $34.50 which is equal to the fair market value of the common stock on the date of grant. It vests as to 25% of the shares of common stock over the four-year period commencing with the date of grant, subject to such individual's continued service on the Board.

INFORMATION CONCERNING BOARD AND COMMITTEE MEETINGS AND COMMITTEES OF THE BOARD

The Board of Directors oversees the business and affairs of the Company and monitors the performance of management. In accordance with corporate governance principles, the Board does not involve itself in day-to-day operations. During

the year ended December 31, 2000, there were five meetings of the Company's Board. The Board also took certain actions by unanimous written consent. No incumbent director attended fewer than 75% of the total number of meetings of the Board and of the Committees of the Board on which he served, except for Dr. DeVita who attended four of the total number of meetings of the Board and of the Committees of the Board on which he served.

The Company has an Executive Committee of the Board composed of Samuel D. Waksal (Chairman), Robert F. Goldhammer and Harlan W. Waksal. The Executive Committee acts for the Board when formal Board action is required between Board meetings. The Executive Committee has all the power of the full Board in the management of the business and affairs of the Company, except those powers that by law cannot be delegated by the Board. The Executive Committee did not meet formally during the year ended December 31, 2000.

The Company has an Audit Committee of the Board composed of Paul B. Kopperl (Chairman), Richard Barth and William R. Miller. The primary functions of the Audit Committee are to monitor the integrity of the Company's financial reporting process and systems of internal controls regarding finance, accounting and legal compliance. The Audit Committee provides an avenue of communication among the independent auditors, management and the Board of Directors. The Audit Committee met three times during the year ended December 31, 2000.

The Company has a Compensation and Stock Option Committee (the "Compensation Committee") of the Board composed of Robert F. Goldhammer (Chairman), Paul B. Kopperl, David M. Kies and Richard Barth. The Compensation Committee is responsible for developing executive compensation policies. The Compensation Committee also (i) determines annually the base salary to be paid to the Chief Executive Officer and determines bonuses and incentive awards to be paid from time to time to the Chief Executive Officer; and (ii) approves annually a salary plan for other senior officers (on the recommendation of the Chief Executive Officer in conjunction with other senior personnel) and approves bonuses and incentive awards to be paid from time to time to such senior officers. The Compensation Committee also administers the Company's various stock option and purchase plans, including the granting of options under the option plans. The Compensation Committee met one time during the year ended December 31, 2000 and also took certain actions by unanimous written consent.

The Company has a Nominating and Corporate Governance Committee composed of David M. Kies (Chairman), Paul B. Kopperl, John Mendelsohn, William R. Miller, Robert F. Goldhammer and Harlan W. Waksal. The Nominating and Corporate Governance Committee considers and makes recommendations to the Board regarding Board and committee nominees and membership, director performance and officer candidates. The Nominating and Corporate Governance Committee also considers and makes recommendations to the Board with respect to corporate organizational and governance matters. The Nominating and Corporate Governance Committee met one time during the year ended December 31, 2000. The Nominating and Corporate Governance Committee considers nominations for director made by stockholders of the Company in accordance with the procedures for submission of proposals at annual or special meetings of stockholders set forth in the Company's Amended and Restated By-laws.

The Company has a Research Oversight Committee composed of Samuel D. Waksal (Chairman), Vincent T. DeVita, Jr., John Mendelsohn and Harlan W. Waksal. The Research Oversight Committee participates on behalf of the Board in monitoring the research focus of the Company. The Research Oversight Committee did not meet formally during the year ended December 31, 2000.

INFORMATION CONCERNING OFFICERS

Certain information concerning officers of the Company is provided below.

SAMUEL D. WAKSAL, PH.D., is the President and Chief Executive Officer of the Company. Certain information concerning Dr. Waksal appears on page 7.

HARLAN W. WAKSAL, M.D., is the Executive Vice President and Chief Operating Officer of the Company. Certain information concerning Dr. Waksal appears on page 7.

PETER BOHLEN, PH.D., 58, has been Senior Vice President, Research of the Company since January 2001. He joined the Company in September 1996 as Vice President, Research. From November 1995 to July 1996 he was Senior Director of Ixsys, a privately-held biotechnology company. From October 1987 to June 1996 he was department head of the Molecular Biology Section of American Cyanamid's Medical Research Division and director of the company's angiogenesis program. He also has held academic positions at the Salk Institute, San Diego and the University of Zurich, Switzerland. Dr. Bohlen received his Ph.D. in chemistry from the University of Berne in Switzerland. In 1983, he received the Cloetta Award in Switzerland for his contributions in the field of protein analysis. He has authored or co-authored over 200 publications and is a named inventor on 26 patents.

CHARLES DUNNE, 36, has been Vice President, Management Information Systems and Facilities since January 2001. Mr. Dunne, one of the Company's first employees, joined the Company in 1984 and has served it in a number of capacities, including Assistant Vice President, Management Information Systems and Facilities during 2000, Senior Director, Management Information Systems during 1999 and Director, Management Information Systems during 1998. Mr. Dunne supervised the construction of the Company's corporate headquarters and research laboratories and has implemented all systems at the Company since 1984.

PAUL A. GOLDSTEIN, 36, has been Vice President, Financial Operations since January 2001. He joined the Company in January 1992 and has served in various capacities since that date, including Assistant Vice President, Finance during 2000, Senior Director, Finance and Controller from January 1998 through December 1999 and Controller from January 1995 through December 1997. Prior to joining the Company he was employed by Laventhol & Horwath, a certified public accounting firm in New York City. Mr. Goldstein is a certified public accountant.

JOHN B. LANDES, 53, has served as Senior Vice President, Legal since January 2001 and General Counsel since 1992. He was Vice President, Legal from 1992 to 2000 and also Vice President, Business Development from 1992 through 1999. Prior thereto, he was Vice President, Administration and Legal since December 1984. He also has been Secretary of the Company since April 1985 and served as its Treasurer from April 1984 through September 1991, except for an interim period from December 1988 to February 1991. From 1978 to 1984, Mr. Landes was an associate attorney with the Boston law firm of Mahoney, Hawkes and Goldings.

LILY WAIYEE LEE, PH.D., 45, joined the Company in April 2001 as its Vice President, Regulatory. Dr. Lee was employed at The Lipsome Company, Division of Elan Corporation, as its Vice President, Clinical & Regulatory Operations and Biostatistics from 1995 to April 2001 and as its Executive Director, Biostatistics and Data Management from 1993 through 1994. Prior to that time she was employed for over five years in various statistical positions at Ciba Consumer Pharmaceuticals, Division of Ciba Geigy. Dr. Lee earned a bachelor

degree in statistics from the University of Minnesota and both a masters degree in Biostatistics and Ph.D. in Demography from the University of California, Berkeley.

DANIEL S. LYNCH, 43, joined the Company in April 2001 as its Vice President, Finance and Chief Financial Officer. From May 1999 through March 2001, he served as Chief Financial Officer of Derby Cycle Corporation. Prior to this, Mr. Lynch served for 15 years in various capacities at Bristol-Myers Squibb Company, including from December 1998 through May 1999, as its Vice President, Finance, U.S. Pharmaceutical, Worldwide Medicines Group; from April 1998 through November 1998 as its Vice President, Finance, Technical Operations, Worldwide Medicines Group; from July 1997 through March 1998 as its Vice

President, Finance, Intercontinental, Worldwide Medicines Group; and from February 1995 through June 1997 as its Vice President, Finance, Worldwide Consumer Medicines Group.

RONALD A. MARTELL, 39, has served as the Company's Vice President, Marketing and Sales since November 1998. Prior to joining the Company he worked at Genentech, Inc. for ten years where he held various positions. Most recently, from 1996 until joining the Company, he served as Genentech's Group Manager of Oncology Products where he directed the launch of Herceptin, Genentech's monoclonal antibody product approved to treat breast cancer. From 1995 to 1996 he served as Senior Product Manager where he launched Pulmozyme for cystic fibrosis in Europe. From 1994 through 1995 he served as Manger of Genentech's Piedmont Sales Division. Prior to that, he served from 1993 as Associate Product Manager for Genentech's Pulmozyme.

MICHAEL NEEDLE, M.D., 41, has served as the Company's Vice President, Clinical Affairs since January 2001. He joined the Company in April 2000 as its Assistant Vice President, Clinical Affairs. Prior to joining the Company, Dr. Needle served as Director, Oncology Clinical Research of G.D. Searle, a Monsanto Company. From July 1993 through November 1997 Dr. Needle served as Assistant Professor of Pediatrics and Neurology, Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine. Dr. Needle received a Bachelor of Arts degree in Physics from Binghamton University and a Doctor of Medicine degree from the State University of New York, Health Science Center at Brooklyn. Dr. Needle performed his residency in Pediatrics at Kings County Hospital in Brooklyn and his Pediatric Hematology/Oncology fellowship at the Fred Hutchinson Cancer Research Center in Seattle and the University of Texas, MD Anderson Cancer Center in Houston.

GARY PAULTER, 38, has served as the Company's Vice President, Engineering and Facilities at its New Jersey location since January 2001. Mr. Paulter joined the Company in 1993 as Facilities Engineer and has served in various capacities since that date, including, Facility Manager from 1995 through 1996, Manager, Engineering & Facilities from 1997 through 1999 and Director, Engineering and Facilities from 1999 through 2000.

ANDREA F. RABNEY, 34, has served as the Company's Vice President, Corporate Communications since January 2001. She joined the Company in 1993 as its Director, Corporate Development and Investor Relations and has served in several other managerial positions since that time, including Senior Director, Corporate Development & Investor Relations from 1998 to 1999 and Assistant Vice President, Corporate Communications during 2000. Prior to joining ImClone Systems, Ms. Rabney served as a compliance analyst at Smith Barney Shearson Inc. (now Salomon Smith Barney) where she was responsible for defining capital markets guidelines

and procedures for foreign and institutional accounts and trading desks. Ms. Rabney holds a law degree from the Jacob D. Fuchsberg Law Center of Touro College.

S. JOSEPH TARNOWSKI, PH.D., 47, has served as the Company's Vice President, Product and Process Development since January 1999. Prior to joining the Company, he held various positions with CellPro, Inc., the principal business of which was the development, manufacture and marketing of automated systems that utilize monoclonal antibodies to purify large quantities of specific cells for therapeutic and diagnostic applications. He joined CellPro in June 1992 as Vice President of Operations, was appointed to Vice President of Research and Development in June 1995 and became Senior Vice President and Chief Technical Officer in December 1996. From November 1986 to May 1992, Dr. Tarnowski was Director, Process and Product Development of Scios Nova Inc. (formerly California Biotechnology Inc.), a company that develops recombinant human proteins for therapeutic uses. Dr. Tarnowski received a Ph.D. in Biochemistry from the University of Tennessee in 1979 and was a Postdoctoral Fellow at the Roche Institute of Molecular Biology from 1979 through 1981.

CATHERINE M. VACZY, 39, has served as the Company's Associate General Counsel since February 1997 and Vice President, Legal since January 2001. She served as its Assistant Vice President, Legal during 2000 and as its Senior Director, Legal, from 1997 through 1999. Prior to joining the Company, Ms. Vaczy served as a senior associate specializing in corporate and securities matters in the New York City office of Ross & Hardies, a Chicago-based law firm.

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LARRY WITTE, 56, has served as the Company's Vice President, Research since January 2001. He joined the Company in 1990 and has served in various capacities since that date, including Assistant Vice President, Research during 2000, Senior Director, Research during 1999 and Director, Research from 1994 to 1999. Since 1990, Dr. Witte has served as an Adjunct Professor of Anatomy and Cell Biology at Columbia University's College of Physicians and Surgeons. Dr. Witte oversees the Company's research activities relating to its Molecular and Cell Biology Laboratory. Dr. Witte is an authority in the areas of molecular and cell biology and cancer research and has authored or co-authored over 45 publications. Dr. Witte earned his Bachelor of Science degree in zoology and his Ph.D. in Physiology from Iowa State University; he did his postdoctoral in cell biology at Columbia's College of Physicians and Surgeons and completed a research fellowship in cell biology at the Mayo Clinic.

SECTION 16(a) BENEFICIAL OWNERSHIP REPORTING COMPLIANCE

Ownership of and transactions in the Company's securities by executive officers and directors of the Company and owners of 10% or more of the Company's outstanding common stock are required to be reported to the SEC pursuant to Section 16(a) of the Exchange Act. During the year ended December 31, 2000, based on information received by the Company, one form was untimely filed for each of Dr. Harlan Waksal, Mr. Robert F. Goldhammer, Mr. William Miller, Dr. Arnold J. Levine and two forms were untimely filed for Dr. Samuel Waksal.

CERTAIN TRANSACTIONS

During the year ended December 31, 2000, the Company paid Dr. Vincent T. DeVita, Jr., a Director of the Company, a total of $100,000 for scientific consulting services provided to the Company by Dr. DeVita.

The Company has accepted from its President and Chief Executive Officer, a

full recourse, unsecured promissory note dated as of December 21, 2000 in the principal amount of $282,200. The note is payable upon the earlier of June 21, 2001 or demand by the Company and bears interest at an annual rate of 10 1/2% for the period that the loan is outstanding.

In January 1998, the Company accepted a full recourse, unsecured promissory note totaling approximately $131,000 from its President and Chief Executive Officer in connection with the exercise of a warrant to purchase 174,610 shares of the Company's common stock. The note was due no later than two years from issuance. Interest was payable on the first anniversary date of the promissory note and on the stated maturity or any accelerated maturity at the annual rate of 8 1/2%. The note, including all interest, has been paid in full.

The Company uses Concord Investment Management, a New York-based money management firm, to manage a substantial portion of the Company's debt security portfolio. The Company's Chairman of the Board is a limited partner of Concord Investment Management. The Company paid investment management fees to Concord Investment Management of approximately $412,000 in the year ended December 31, 2000.

EXECUTIVE COMPENSATION

REPORT OF COMPENSATION COMMITTEE

Overall Philosophy

The Company's executive compensation philosophy is based on the premise that compensation should be set at levels that support the Company's business strategies and long-term objectives and relate to an individual's performance. The elements of the executive compensation package are base salary and participation in annual incentives, including stock options.

In establishing base salaries, annual incentive awards and awards of stock options, the Compensation Committee considers the executive's annual review and periodic compensation surveys, including those provided by third parties covering the biopharmaceutical industry.

The Compensation Committee uses no set formulas and may accord different weight to different factors for each executive. The Committee looks toward the progress of the Company's research and development programs, its ability to gain support for such programs, either internally or externally, its ability to attract, motivate and retain talented employees and its ability to secure capital sufficient for its product development to achieve rapid and effective commercialization as may be practicable.

Deductibility of Compensation

The Compensation Committee has reviewed the impact of Section 162(m) of the Internal Revenue Code of 1986, as amended (the "Code"), which, beginning in 1994, limits the deductibility of certain otherwise deductible compensation in excess of $1 million paid to the Chief Executive Officer and the other Named Officers (as hereinafter defined). It is the policy of the Company to attempt to have its executive compensation plans treated as tax deductible compensation whenever, in the judgment of the Compensation Committee, to do so would be consistent with the objectives of that compensation plan.

Chief Executive Officer Compensation

In evaluating Dr. Samuel D. Waksal's 2000 performance, the following Company achievements were noted:

- In November 2000, the Company announced favorable preliminary results from its Phase II study of IMC-C225 in combination with irinotecan in refractory colorectal carcinoma and that it had met its primary endpoint of patient response

- At the May 2000 meeting of the American Society of Clinical Oncologists ("ASCO"), the Company gave presentations of data on the use of IMC-C225 and chemotherapy in the treatment of colorectal and head and neck refractory cancers

- During 2000, the Company continued to move toward the filing of a Biologics License Application ("BLA") with the Food and Drug Administration for its Phase II study of IMC-C225 in combination with irinotecan in refractory colorectal carcinoma

- In 2000, the Company commenced patient treatment in a Phase I clinical study of its lead clinical candidate for angiogenesis inhibition, IMC-1C11 in patients with metastatic colorectal carcinoma

- At the end of 2000, the Company had financial assets of approximately $370,000,000, of which $240,000,000 resulted from the February 2000 private placement of the Company's 5 1/2% convertible notes due 2005. These resources enable the Company to pursue its established strategic goals

The Company's leadership under both Dr. Samuel D. Waksal and Dr. Harlan W. Waksal has resulted in the Company continuing to progress toward becoming a commercial stage, fully integrated biopharmaceutical company.

Compensation and Stock Option Committee

Robert F. Goldhammer, Chairman
Richard Barth
David M. Kies
Paul B. Kopperl

COMPENSATION COMMITTEE INTERLOCKS AND INSIDER PARTICIPATION

As of December 31, 2000, the members of the Compensation Committee were Richard Barth, Robert F. Goldhammer (Chairman), David M. Kies and Paul B. Kopperl, none of whom is a full-time employee of the Company or any of its subsidiaries or has ever been an officer of the Company or any subsidiaries.

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SUMMARY COMPENSATION TABLE

The Summary Compensation Table sets forth the cash and non-cash compensation awarded to, earned by, or paid to the Company's Chief Executive Officer and the four most highly compensated officers (other than the Chief Executive Officer) for the years ended December 31, 2000, 1999 and 1998 who were serving as officers at December 31, 2000 and whose total salary and bonus exceeded $100,000 for the year ended December 31, 2000 (the "Named Officers").

<TABLE>
<CAPTION>

		ANNUAL COMPENSATION		
	YEAR	SALARY ($)(1)	BONUS ($)(2)	OTHER ANNUAL COMPENSATION ($)(3)
<S>	<C>	<C>	<C>	<C>
Samuel D. Waksal.....	2000	$500,000	$1,000,000	$ --
President and Chief	1999	300,000	600,000	--
Executive Officer	1998	300,000	400,000	--
Harlan W. Waksal.....	2000	400,000	800,000	--
Executive Vice President and Chief Operating	1999	250,000	500,000	--
Officer	1998	250,000	300,000	--
S. Joseph Tarnowski(6).....	2000	204,750	100,000	36,083(9)
Vice President, Product	1999	195,000	60,000	--
and Process Development	1998	--	--	--
John B. Landes.....	2000	200,000	100,000	--
Senior Vice President,	1999	175,000	25,000	--
Legal and General Counsel	1998	165,000	120,000	--
Ronald A. Martell(7).....	2000	183,750	100,000	--
Vice President,	1999	175,000	100,000	--
Marketing and Sales	1998	15,417(7)	25,000(8)	161,216(9)

</TABLE>

(1) Amounts shown include compensation deferred pursuant to Section 401(k) of the Code.

(2) Although the Company has no formal bonus plan, the Compensation Committee, in its discretion, may award bonuses to officers of the Company. The Company has paid bonuses based on individual and Company performance. Amounts shown include awards paid relative to services rendered in each of the last three fiscal years. All bonus awards for each of the last three fiscal years were paid in cash. Bonuses are recorded for the period in which they were earned.

(3) Excludes perquisites and other personal benefits for each Named Officer which did not equal or exceed the lesser of $50,000 or 10% of such individual's base salary and bonus for the years ended December 31, 2000, 1999 and 1998, respectively.

(4) Options to purchase the number of shares of common stock shown are recorded for the period in which they were granted.

(5) Consists of premium payments on a term life insurance policy for Dr. Samuel D. Waksal under which his daughters are the beneficiaries.

(6) Dr. Tarnowski commenced employment with the Company in January 1999.

(7) Mr. Martell commenced employment with the Company in November 1998.

(8) This was a sign-on bonus paid to Mr. Martell upon his joining the Company.

(9) Consists of relocation expenses associated with the individual's joining the Company.

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OPTION GRANTS IN FISCAL 2000

The following table sets forth certain information relating to stock option grants to the Named Officers during the year ended December 31, 2000.

<TABLE>
<CAPTION>

NAME	NUMBER OF SECURITIES UNDERLYING OPTIONS GRANTED#	% OF TOTAL OPTIONS GRANTED TO EMPLOYEES IN FISCAL YEAR(1)	EXERCISE PRICE ($/SHARE)(2)	EXPIRATION DATE	POTEN AS STOCK 0%($)
<S>	<C>	<C>	<C>	<C>	<C>
Samuel D. Waksal.....	--	--	--	--	--
Harlan W. Waksal.....	--	--	--	--	--
John B. Landes.....	34,000(4)	1%	$31.8125	12/20/10	--
S. Joseph Tarnowski....	24,000(4)	1%	$31.8125	12/20/10	--
Ronald A. Martell.....	24,000(4)	1%	$31.8125	12/20/10	--

</TABLE>

(1) The Company granted options to purchase a total of 2,585,220 shares of common stock to employees during 2000.

(2) Options were granted to purchase common stock at an exercise price that equaled the fair market value of the common stock on the date of grant.

(3) The amounts set forth in the three columns represent hypothetical gains that might be achieved by the holders if the respective options are exercised at the end of their terms. These gains are based on assumed rates of stock price appreciation of 0%, 5% and 10% compounded annually from the dates the respective options were granted.

(4) These options are exercisable as to 50% of the shares on each of the first and second anniversaries of the date of grant, except that 10,000 of the options held by Mr. Landes are exercisable as to 25% of the shares on each of the first, second, third and fourth anniversaries of the date of grant.

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OPTION AND WARRANT EXERCISES AND VALUES FOR FISCAL 2000

The following table sets forth option and warrant exercises during the year ended December 31, 2000 by the Named Officers and the value of the options and warrants held by such person on December 31, 2000, whether or not exercisable on such date.

<TABLE>
<CAPTION>

NAME	SHARES ACQUIRED ON EXERCISE(#)	VALUE REALIZED($)(1)	NUMBER OF SHARES UNDERLYING UNEXERCISED OPTIONS/ WARRANTS AT DECEMBER 31, 2000(#)	
			EXERCISABLE	UNEXERCISABLE

<S>	<C>	<C>	<C>	<C>
Samuel D. Waksal.....	1,450,000	$54,541,150	2,120,000	180,000
Harlan W. Waksal.....	6,360	306,120	2,430,000	150,000
John B. Landes.....	298,000	12,019,938	209,000	115,000
S. Joseph Tarnowski.....	14,000	560,170	23,500	136,500
Ronald A. Martell.....	15,000	859,375	82,500	196,500

</TABLE>

(1) The values realized were calculated by multiplying the closing market price of the common stock on the date of exercise by the respective number of shares exercised and subtracting the aggregate exercise price. Accordingly, such values realized assume a sale of such common stock on the date of exercise, however, only 9% of these shares were sold as of April 23, 2001.

(2) The values were calculated by multiplying the closing market price of the common stock on December 31, 2000 ($44.00 per share as reported by the Nasdaq National Market on that date) by the respective number of shares and subtracting the aggregate exercise price, without making any adjustments for vesting, termination contingencies or other variables. If the exercise price of an option or warrant is equal to or greater than $44.00 the option or warrant is deemed to have no value.

OTHER BENEFIT PLANS

The Company has no defined benefit or defined contribution retirement plans other than the ImClone Systems Incorporated 401(k) Employee Savings Plan (the "Plan") established under Section 401(k) of the Code. Contributions to the Plan are voluntary, and substantially all full-time employees are eligible to participate. For 2000, the Company elected to make voluntary matching contributions equal to 25% of the first 4% of an employee's eligible compensation contributed by the employee, limited to $2,500 per employee. The Company made such a matching contribution for 2000 which totaled $108,000. The Company anticipates evaluating the level of its matching contribution, if any, on an annual basis. For 2001, the Company increased the voluntary matching contribution to 25% of the first 6% of an employee's eligible compensation contributed by the employee, limited to $2,500 per employee.

COMMON STOCK PRICE PERFORMANCE

The graph below provides a comparison of the cumulative total return (assuming reinvestment of dividends) for the Company (which paid no dividends) with The Nasdaq Stock Market (U.S. Companies) Total Return Index and The Nasdaq Pharmaceutical Stocks Total Return Index for the period from December 31, 1995 through December 31, 2000. The graph assumes $100 was invested in ImClone common stock and each of the indexes at the beginning of such period. The Nasdaq Stock Market (U.S. Companies) Total Return Index comprises all domestic common shares traded on the Nasdaq National Market and the Nasdaq SmallCap Market. The Nasdaq Pharmaceutical Stocks Total Return Index represents all companies, including biotechnology companies, trading on Nasdaq classified under the Standard Industrial Classification Code for pharmaceuticals.

COMPARISON OF FIVE YEAR TOTAL RETURN AMONG IMCLONE COMMON STOCK,
NASDAQ STOCK MARKET (U.S. COMPANIES) TOTAL RETURN INDEX
AND NASDAQ PHARMACEUTICAL STOCKS TOTAL RETURN INDEX

<TABLE>
<CAPTION>

	IMCLONE SYSTEMS	NASDA
<S>	<C>	<C>
12/31/95	100	
12/31/96	128	
12/31/97	107	
12/31/98	119	
12/31/99	520	
12/31/00	577	

</TABLE>

REPORT OF THE AUDIT COMMITTEE

Notwithstanding anything to the contrary set forth in any of the Company's previous or future filings under the Securities Act of 1933, as amended or the Exchange Act that might incorporate this proxy statement or future filings with the SEC, in whole or in part, the following report shall not be deemed to be incorporated by reference into any such filing.

MEMBERSHIP AND ROLE OF THE AUDIT COMMITTEE

The Audit Committee (the "Audit Committee") consists of the following members of the Company's Board of Directors: Paul B. Kopperl, Chairman, Richard Barth and William R. Miller. During 2000, Vincent T. DeVita, Jr. also served on the Audit Committee. Each of the members of the Audit Committee is "independent" as defined under the National Association of Securities Dealers' listing standards. The Audit Committee operates under the written charter adopted by the Board of Directors which is included in this proxy statement as Appendix A.

The primary functions of the Audit Committee are to monitor the integrity of the Company's financial reporting process and systems of internal controls regarding finance, accounting and legal compliance and to provide an avenue of communication among the independent auditors, management and the Board of Directors. The primary duties and responsibilities of the Audit Committee are to (i) review the Company's annual audited financial statements prior to filing with the SEC or distribution to the public; (ii) in consultation with management and the independent auditors, consider the integrity of the Company's financial reporting procedures and controls; (iii) review with management and the independent auditors the Company's quarterly financial statements prior to filing with the SEC or distribution to the public; (iv) periodically perform self-assessment of Audit Committee performance; (v) annually review policies and procedures as well as test results associated with directors' and officers' expense accounts and perquisites; and (vi) annually review a summary of directors' and officers' related party transactions and potential conflicts of interest. The Audit Committee also reviews the performance of the independent auditors and their fees and recommends their selection and engagement to the Board of Directors.

REVIEW OF THE COMPANY'S AUDITED FINANCIAL STATEMENTS FOR THE FISCAL YEAR ENDED DECEMBER 31, 2000.

The Audit Committee reviewed and discussed the audited financial statements of the Company for the fiscal year ended December 31, 2000 with the Company's management and with KPMG LLP, the Company's certified independent public accountants. Such review and discussions included the matters required to be

discussed by Statement on Auditing Standards No. 61 (Communication with Audit Committees).

The Audit Committee also reviewed the written disclosures and the letter from KPMG LLP required by Independence Standards Board Standard No. 1 (Independence Discussion with Audit Committees) and discussed the independence of KPMG LLP with the Company's management and with that firm.

Based on the Audit Committee's review and discussions noted above, the Audit Committee recommended to the Board of Directors that the Company's audited financial statements be included in the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2000 for filing with the SEC. The Audit Committee and Board of Directors have recommended, subject to ratification by the stockholders, that KPMG LLP be selected as the Company's independent certified public accountants for the fiscal year ending December 31, 2001.

The Audit Committee held three meetings during the fiscal year ended December 31, 2000. The meetings were designed to facilitate and encourage private communication among members of the Audit Committee, the Company's independent certified public accountants and the Company's internal staff responsible for accounting and legal matters.

Audit Committee

Paul B. Kopperl, Chairman
William R. Miller
Richard Barth

PROPOSAL NO. 2

RATIFICATION OF INDEPENDENT CERTIFIED PUBLIC ACCOUNTANTS

The Audit Committee and the Board have selected KPMG LLP as independent certified public accountants for the Company for the year ending December 31, 2001. KPMG LLP has served as the Company's auditor since 1988. The ratification of the selection of independent certified public accountants is to be voted upon at the meeting, and it is intended that the persons named in the accompanying proxy will vote for KPMG LLP. Representatives of KPMG LLP are expected to attend the meeting, to have an opportunity to make a statement if they desire to do so and to be available to respond to appropriate questions.

AUDIT FEES

The aggregate fees billed by KPMG LLP in connection with its audit of the Company's annual financial statements for the year 2000 and its review of the financial statements included in the Company's Form 10-Qs during 2000 was $88,300.

FINANCIAL INFORMATION SYSTEMS DESIGN AND IMPLEMENTATION FEES

The Company did not engage KPMG LLP to provide services for the Company regarding financial information systems design and implementation during 2000.

ALL OTHER FEES

KPMG LLP billed the Company fees totaling $149,040 for all other services performed during 2000 which related to tax consulting and compliance; the

Company's February 2000 offering of 5 1/2% convertible notes; various other SEC filings; and various technical accounting consultation. The Audit Committee has considered whether the provision of all other services by KPMG LLP is compatible with maintaining KPMG LLP's independence and concluded that KPMG LLP is "independent".

THE BOARD RECOMMENDS A VOTE "FOR" THE RATIFICATION OF THE SELECTION OF KPMG LLP TO ACT AS THE COMPANY'S INDEPENDENT CERTIFIED PUBLIC ACCOUNTANTS FOR THE YEAR ENDING DECEMBER 31, 2001 (PROPOSAL NO. 2 ON YOUR PROXY CARD).

STOCKHOLDER PROPOSALS

A stockholder proposal intended to be presented at the Company's Annual Meeting of Stockholders to be held in 2002 must be received by the Company on or before January 1, 2002 in order to be included in the Company's proxy statement and form of proxy relating to that meeting.

Please complete, sign and date the enclosed proxy card, which is revocable as described herein, and mail it promptly in the enclosed postage-paid envelope.

By Order of the Board of Directors

/s/ John B. Landes
John B. Landes
Secretary

New York, New York
April 23, 2001

IT IS IMPORTANT THAT PROXIES BE RETURNED PROMPTLY. WE URGE YOU TO FILL IN, SIGN AND RETURN THE ACCOMPANYING PROXY CARD NO MATTER HOW LARGE OR SMALL YOUR HOLDINGS MAY BE.

APPENDIX A

IMCLONE SYSTEMS INCORPORATED

CHARTER OF THE AUDIT COMMITTEE OF THE BOARD OF DIRECTORS

I. AUDIT COMMITTEE PURPOSE

The Audit Committee is appointed by the Board of Directors to assist the Board in fulfilling its oversight responsibilities. The Audit Committee's primary duties and responsibilities are to:

- Monitor the integrity of the Company's financial reporting process and systems of internal controls regarding finance, accounting, and legal compliance.

- Monitor the independence and performance of the Company's independent auditors.

- Provide an avenue of communication among the independent auditors, management, and the Board of Directors.

The Audit Committee has the authority to conduct any investigation appropriate to fulfilling its responsibilities, and it has direct access to the

independent auditors as well as anyone in the organization. The Audit Committee has the ability to retain, at the Company's expense, special legal, accounting, or other consultants or experts it deems necessary in the performance of its duties.

II. AUDIT COMMITTEE COMPOSITION AND MEETINGS

Audit Committee members shall meet the requirements of the NASD. The Audit Committee shall be comprised of three or more directors as determined by the Board, each of whom shall be independent non-executive directors, free from any relationship that would interfere with the exercise of his or her independent judgment. All members of the Committee shall have a basic understanding of finance and accounting and be able to read and understand fundamental financial statements, and at least one member of the Committee shall have accounting or related financial management expertise.

Audit Committee members shall be appointed by the Board. If an audit committee Chair is not designated or present, the members of the Committee may designate a Chair by majority vote of the Committee membership.

The Committee shall meet approximately three times annually, or more frequently as circumstances dictate. The Audit Committee Chair shall prepare and/or approve an agenda in advance of each meeting. The Committee should meet privately in executive session at least annually with management, the independent auditors, and as a committee to discuss any matters that the Committee or each of these groups believe should be discussed. In addition, the Committee, or at least its Chair, should communicate with management and the independent auditors quarterly to review the Company's financial statements and significant findings based upon the auditor's review procedures.

III. AUDIT COMMITTEE RESPONSIBILITIES AND DUTIES

Review Procedures

1. Review and reassess the adequacy of this Charter at least annually. Submit the Charter to the Board of Directors for approval and have the document published in accordance with Securities and Exchange Commission regulations.

2. Review the Company's annual audited financial statements prior to filing or distribution. Review should include discussion with management and independent auditors of significant issues regarding accounting principles, practices, and judgments.

3. In consultation with management and the independent auditors, consider the integrity of the Company's financial reporting processes and controls. Discuss significant financial risk exposures and

the steps management has taken to monitor, control, and report such exposures. Review significant findings prepared by the independent auditors together with management's responses.

4. Review with financial management and the independent auditors the Company's quarterly financial results prior to the release of earnings and/or the Company's quarterly financial statements prior to filing or distribution. Discuss any significant changes to the Company's accounting principles and any items required to be communicated by the independent auditors in accordance with SAS 61. The Chair of the

Committee may represent the entire Audit Committee for purposes of this review.

5. Periodically perform self-assessment of Audit Committee performance.

6. Annually review policies and procedures as well as test results associated with directors' and officers' expense accounts and prerequisites. Annually review a summary of directors' and officers' related party transactions and potential conflicts of interest.

Independent Auditors

7. The independent auditors are ultimately accountable to the Audit Committee and the Board of Directors. The Audit Committee shall review the independence and performance of the auditors and annually recommend to the Board of Directors the appointment of the independent auditors or approve any discharge of auditors when circumstances warrant.

8. On an annual basis, the Committee should review and discuss with the independent auditors all significant relationships they have with the Company that could impair the auditors' independence.

9. Review the independent auditors audit plan -- discuss scope, staffing, locations, reliance upon management, and general audit approach.

10. Prior to releasing the year-end earnings, discuss the results of the audit with the independent auditors. Discuss certain matters required to be communicated to audit committees in accordance with AICPA SAS 61.

11. Consider the independent auditors' judgments about the quality and appropriateness of the Company's accounting principles as applied in its financial reporting.

Legal Compliance

12. On at least an annual basis, review with the Company's counsel, any legal matters that could have a significant impact on the organization's financial statements, the Company's compliance with applicable laws and regulations, and inquiries received from regulators or governmental agencies.

Other Audit Committee Responsibilities

13. Annually prepare a report to shareholders as required by the Securities and Exchange Commission. The report should be included in the Company's annual proxy statement.

14. Perform any other activities consistent with this Charter, the Company's by-laws, and governing law, as the Committee or the Board deems necessary or appropriate.

15. Maintain minutes of meetings and periodically report to the Board of Directors on significant results of the foregoing activities.

Appendix B

IMCLONE SYSTEMS INCORPORATED

Dear Stockholder:

Please take note of the important information enclosed with this Proxy Ballot. There are a number of issues related to the management and operation of your Company that require your immediate attention and approval. These are discussed in detail in the enclosed proxy materials.

Your vote counts, and you are strongly encouraged to exercise your right to vote your shares.

Please mark the boxes on this proxy card to indicate how your shares shall be voted, then sign the card, detach it and return your proxy vote in the enclosed postage paid envelope.

Your vote must be received prior to the Annual Meeting of Shareholders, May 24, 2001.

Thank you in advance for your prompt consideration of these matters.

Sincerely,

ImClone Systems Incorporated

IMCLONE SYSTEMS INCORPORATED

PROXY FOR THE MEETING OF STOCKHOLDERS, MAY 24, 2001
THIS PROXY IS SOLICITED ON BEHALF OF THE BOARD OF DIRECTORS

The undersigned hereby appoints Robert F. Goldhammer, John B. Landes and Samuel D. Waksal as Proxies each with power of substitution and hereby authorizes each of them to represent and to vote, as designated below, all the shares of Common Stock of ImClone Systems Incorporated held of record by the undersigned on April 9, 2001 at the Annual Meeting of Stockholders to be held at 10:00 a.m. on May 24, 2001 or any adjournment thereof.

PLEASE MARK, SIGN, DATE AND RETURN THIS PROXY TO EQUISERVE, THE COMPANY'S TRANSFER AGENT, TO BE RECEIVED NO LATER THAN MAY 23, 2001.

This Proxy when properly executed will be voted in the manner directed herein by the undersigned stockholder. IF NO DIRECTION IS MADE, THIS PROXY WILL BE VOTED FOR PROPOSALS 1,2 and 3.

PLEASE VOTE, DATE AND SIGN ON REVERSE AND RETURN PROMPTLY IN THE ENCLOSED ENVELOPE

NOTE: PLEASE SIGN EXACTLY AS YOUR NAME(S) APPEAR(S) ON THIS CARD. ALL JOINT OWNERS SHOULD SIGN. WHEN SIGNING AS EXECUTOR, ADMINISTRATOR, ATTORNEY, TRUSTEE OR GUARDIAN OR AS CUSTODIAN FOR A MINOR, PLEASE GIVE FULL TITLE AS SUCH. IF A CORPORATION, PLEASE SIGN IN FULL CORPORATE NAME AND INDICATE THE SIGNER'S OFFICE. IF A PARTNER, SIGN THE PARTNERSHIP NAME.

HAS YOUR ADDRESS CHANGED?

DO YOU HAVE ANY COMMENTS?

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[X] PLEASE MARK VOTES AS IN THIS EXAMPLE

Mark box at right if you plan to attend the meeting [ ]

Mark box at right if an address change or comment has been noted on the reverse side of this card [ ]

RECORD DATE SHARES:

1) ELECTION OF DIRECTORS. For: [ ] Withhold: [ ] For All Except: [ ]

Nominees:
Richard Barth
Vincent T. DeVita. Jr.
Robert F. Goldhammer
Paul B. Kopperl
David M. Kies
Arnold Levine
John Mendelsohn
William R. Miller
Harlan W. Waksal
Samuel D. Waksal

NOTE: IF YOU DO NOT WISH YOUR SHARES VOTED "FOR" A PARTICULAR NOMINEE, MARK THE "FOR ALL EXCEPT" BOX AND STRIKE A LINE THROUGH THE NAME(S) OF THE NOMINEE(S). YOUR SHARES SHALL BE VOTED FOR THE REMAINING NOMINEE(S).

2) To ratify the appointment of KPMG LLP to serve as the Company's independent certified public accountants for the fiscal year ending December 31, 2001. For: [ ] Against: [ ] Abstain: [ ]

3) To consider and act upon any other business as may come before the meeting or any adjournment thereof.

[ ] PLEASE CHECK THIS BOX IF YOU EXPECT TO ATTEND THE MEETING

Please be sure to sign and date this Proxy.

Date:

_____
Stockholder sign here

_____
Co-owner sign here
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</SEC-DOCUMENT>
-----END PRIVACY-ENHANCED MESSAGE-----

16

ImClone Systems Incorporated

Special Meeting of the Executive Committee
of the Board of Directors

May 10, 2001

A special meeting of the Executive Committee of the Board of Directors (the "Committee") of ImClone Systems Incorporated (the "Company") was held via teleconference at approximately 4:00 on Thursday, May 10, 2001.

In attendance at the meeting were Dr. Samuel D. Waksal and Mr. Robert F. Goldhammer, constituting two of the three members of the Committee. Dr. Harlan W. Waksal was unable to attend.

The purpose of the meeting was to discuss making a bridge loan of $1,000,000 (the "Loan") to A.C.T. Group, Inc. ("ACT"), a company involved in the emerging fields of genetic programming and cloning. Dr. Waksal described the terms of the Loan substantially as they appear on Attachment A hereto. He also described that the Company would receive a warrant to purchase additional shares as part of the transaction, also substantially as described on Attachment A.

There being no further business to come before the Committee, a motion to adjourn the meeting was made, seconded and so voted and the meeting was declared adjourned.

A true and accurate record:
Attest: _____
Samuel D. Waksal

SUMMARY OF TERMS OF BRIDGE LOAN TO ACT GROUP, INC.

- Loan amount is $1,000,000.
- Loan payable as follows:

(a) If, prior to November 31, 2001, ACT shall have issued shares of its Series B Convertible Preferred Stock (the "Series B Stock"), as described in the Confidential Private Placement Memorandum dated January 31, 2001 (the "Private Placement Memorandum"), in an amount of at least $10 million and otherwise substantially on the terms described in the Private Placement Memorandum (the date of such issuance shall be referred to as the "Series B Closing Date"), the Loan shall be repaid by ACT issuing to ImClone on the Series B Closing Date that number of shares of Series B Stock determined by dividing $1,000,000 by 80% of the per share purchase price paid for the Series B Stock on the Series B Closing Date;

(b) If prior to November 31, 2001, ACT has not effected the issuance of Series B Stock contemplated by Section 3.1(a) but shall have entered into a binding agreement with respect to a merger or other transaction in which the Borrower's stockholders shall receive securities of another entity, and such resulting entity shall have at least $10 million more in cash than did the ACT immediately prior to such transaction, the Loan shall be repaid by ACT issuing to ImClone, immediately prior to the consummation of such transaction, that number of shares of Common Stock by dividing $1,000,000 by $1.60; and

(c) If neither the Series B Closing nor the closing of a transaction contemplated by Section 3.1(b) shall have occurred prior to November 31, 2001, then on November 31, 2001, the Loan shall be repaid by ACT paying to ImClone $1,000,000 in lawful money of the United States; provided that, at ACT's option, ACT may issue and deliver to Lender on November 31, 2001 that number of shares of its Common Stock determined by dividing $1,000,000 by 80% of the issuance price of the Series A Preferred Stock (i.e., $1.60). At such time, ImClone shall also have the right to purchase up to an additional $1,000,000 worth of Common Stock at the same price.

- ACT is subject to standard affirmative and negative covenants.
- The loan agreement provides to ImClone a right of first offer with regard to ACT's stem cell genomics technology.
- The loan agreement requires them to appoint Sam Waksal to the ACT Board.
- In connection with the Loan, ImClone is issued a warrant to purchase shares of ACT's common stock which becomes exercisable upon the earlier of November 31, 2001 or the Series B Closing date and will remain exercisable until the closing of ACT's IPO or November 31, 2006 The warrant is exercisable at the following price: If, prior to November 31, 2001, the ACT shall have issued shares of its Series B Convertible Preferred Stock (the Series B Stock), as described in the Confidential Private Placement Memorandum dated January 31, 2001 (the Private Placement Memorandum"), in an amount of at least $10 million and otherwise substantially on the terms described in the Private Placement Memorandum (the date of such issuance shall be referred to as the "Series B Closing Date"), then the Exercise Price shall be the product of .80 times the original conversion price relating to a share of Series B Stock. If, prior to November 31, 2001, the events described in Section 3.1(a) of the Loan Agreement dated as of May 31, 2001, between ImClone and ACT shall not have occurred, then the Exercise Price shall be the product of .80 times the issuance price of the Series A Preferred Stock (i.e., $1.60), as adjusted from time to time in accordance with Section 3 of the Warrant.

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ImClone Systems Incorporated

Special Telephonic Meeting of the Board of Directors

July 18, 2001

A special telephonic meeting of the Board of Directors of ImClone Systems Incorporated (the "Company") was held pursuant to notice duly given at 5:30 p.m. on July 18, 2001. Participating via teleconference were Mr. Richard Barth, Mr. Robert F. Goldhammer, Mr. David M. Kies, Mr. Paul B. Kopperl, Dr. John Mendelsohn, Mr. William R. Miller, Dr. Harlan Waksal and Dr. Samuel Waksal. Drs. Arnold Levine and Vincent T. DeVita, Jr. were unable to attend. Also participating from the Company's executive offices at 180 Varick Street, New York, New York 10014 were Mr. Daniel Lynch, Vice President, Finance and Chief Financial Officer and Ms. Catherine M. Vaczy, Associate General Counsel. Also present were the Company's advisors, Phillip Mills, Esq., Partner, Davis, Polk & Wardwell and Peter Crnkovich, Managing Director, Morgan Stanley Dean Witter & Co. Dr. Samuel Waksal presided over the meeting and Ms. Vaczy served as Secretary of the meeting.

Dr. Samuel Waksal, together with Mr. Lynch, made a presentation to the group describing the status of negotiations relating to the proposed transaction as currently formulated between the Company and Bristol-Myers Squibb Company ("BMS"). The presentation included a review of all relevant issues relating to the proposed transaction as currently formulated.

Dr. Samuel Waksal noted that he had previously introduced at a prior meeting, Phillip Mills, Partner, Davis Polk & Wardwell and Peter Crnkovich, Managing Director, Morgan Stanley Dean Witter & Co. whose firms were advising the Company with regard to the proposed transaction with BMS. Dr. Samuel Waksal requested that each of Mr. Mills and Mr. Crnkovich present to the Board an overview of the current status of negotiations from a legal and financial perspective, respectively.

After the presentation, relevant questions were posed by the Board members and responded to in full by management, and its advisors.

Dr. Samuel Waksal advised the Board that they would be kept frequently apprised of the status of the negotiations as they progressed.

Messrs. Mills and Crnkovich then left the meeting.

Next, Dr. Samuel Waksal advised the meeting that both he and Dr. Harlan Waksal were interested in obtaining loans from the Company in order to finance the exercise price of their remaining outstanding options. Dr. Samuel Waksal's outstanding and then exercisable options were 2,060,000 exercisable at an aggregate exercise price of $18,178,750 and Dr. Harlan Waksal's outstanding and then exercisable options were 2,080,000 exercisable at an aggregate exercise price of $15,747,550. Dr. Samuel Waksal advised the meeting that the loan was intended to bridge the period from exercise until the tender offer proceeds were received. Dr. Samuel Waksal stated that the loans would be full-recourse, bear a market interest rate which would be adjusted quarterly and have

other arm's length terms and that they would be payable upon the earlier of one year or upon demand by the Company. The Board then discussed in full the making of the loans and approved them on the terms discussed. They also approved such loans to other members of the Board on the same terms.

There being no further business to come before the Board, a motion to adjourn the meeting was made, seconded and so voted and the meeting was declared adjourned at approximately 6:30.

A true and accurate record.

Attest: _____
Catherine M. Vaczy,
Secretary

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ImClone Systems Incorporated

Special Meeting of the Executive Committee
of the Board of Directors

August 7, 2001

A special meeting of the Executive Committee of the Board of Directors (the "Committee") of ImClone Systems Incorporated (the "Company") was held via teleconference at approximately 5:00 on Tuesday, August 7, 2001.

In attendance at the meeting were Dr. Harlan W. Waksal and Mr. Robert F. Goldhammer, constituting two of the three members of the Committee. Dr. Samuel Waksal, the third member of the Committee, recused himself due to the subject matter of the meeting.

The subject of the meeting related to the Company's extending the term of a Promissory Note accepted from Dr. Samuel Waksal in the amount of $282,200. After due discussion, the Committee ratified the extension of the term of the Promissory Note until December 21, 2001 on the same terms as the original Promissory Note.

There being no further business to come before the Committee, a motion to adjourn the meeting was made, seconded and so voted and the meeting was declared adjourned.

A true and accurate record.
Attest: _____
Harlan W. Waksal

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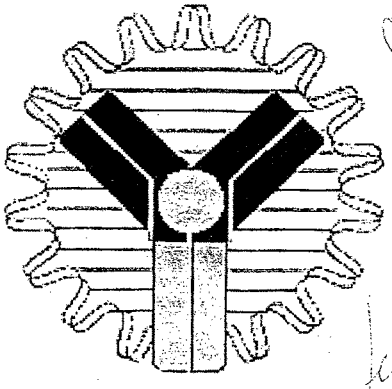

ImClone Systems Incorporated

BOARD OF DIRECTORS HANDBOOK

IMCLONE SYSTEMS INCORPORATED
180 VARICK STREET, 6TH FLOOR
NEW YORK, NY 10014

GENERAL TEL: (212) 645-1405

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SEPTEMBER 2001

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IMCLONE SYSTEMS INCORPORATED
BOARD OF DIRECTORS
DIRECTORY
PAGE 2

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Dr. Harlan W. Waksal ImClone Systems Incorporated 180 Varick Street New York, NY 10014 Tel: (212) 645-1405 Fax: (212) 645-2054	Home:	85 Stonebridge Road Montclair, NJ 07042 Tel: (973) 509-8463 Fax: (973) 509-1784 Cell: (917) 658-6069 Car: (973) 865-5853
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IMCLONE SYSTEMS INCORPORATED

SENIOR MANAGEMENT

Dr. Peter Bohlen	Senior Vice President, Research
Richard Crowley	**Vice President, Manufacturing**
Charles Dunne	Vice President, MIS and Facilities
Paul Goldstein	Vice President, Financial Operations
John B. Landes	Senior Vice President, Legal and General Counsel
Dr. Lily Waiyee Lee	Vice President, Regulatory Affairs and Quality Assurance
Daniel S. Lynch	Vice President, Finance and Chief Financial Officer
Ronald A. Martell	Vice President, Marketing and Sales
Dr. Michael Needle	Vice President, Clinical Affairs
Gary Paulter	Vice President, Engineering and Facilities
Andrea Rabney	Vice President, Corporate Communications
Dr. S. Joseph Tarnowski	Senior Vice President, Product and Process Development
Catherine M. Vaczy	Vice President, Legal and Associate General Counsel
Dr. Harlan W. Waksal	Executive Vice President and Chief Operating Officer
Dr. Samuel D. Waksal	President and Chief Executive Officer
Dr. Larry Witte	Vice President, Research

SENIOR MANAGEMENT DIRECTORY

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Partner
Richard Drucker, Esq.
Partner
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Fax: (212) 450-5500
(Corporate Counsel)

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Partner
Kenyon & Kenyon
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Fax: (212) 344-6235
(Patent Counsel)

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Fax: (609) 896-2968

IMCLONE SYSTEMS INCORPORATED

DIRECTOR -- TERMS

The term of office for all Directors expires annually at each meeting of shareholders.

IMCLONE SYSTEMS INCORPORATED

COMMITTEE ASSIGNMENTS

Executive Committee Members

Samuel D. Waksal, Chairman
Robert F. Goldhammer
Harlan W. Waksal

Audit Committee

Paul B. Kopperl, Chairman
Richard Barth
William R. Miller

Compensation and Stock Option Committee

Robert F. Goldhammer, Chairman
Richard Barth
David M. Kies
Paul B. Kopperl

Nominating and Corporate Governance Committee

David M. Kies, Chairman
Paul B. Kopperl
William R. Miller

Research Oversight Committee

Samuel D. Waksal, Chairman
Vincent T. DeVita, Jr.
Arnold Levine
John Mendelsohn
Harlan W. Waksal

BOARD POLICY - 01

REMUNERATION OF DIRECTORS AND COMMITTEE MEMBERS

1. Directors (not otherwise employed by the Corporation or compensated for providing substantial consulting services to the Corporation) shall receive an annual fee of $10,000. The Chairman (not otherwise employed full-time by the Corporation or compensated for providing substantial consulting services to the Corporation) shall receive an annual fee of $150,000.

   Commencing January 2002, Directors (not otherwise employed by the Corporation or compensated for providing substantial consulting services to the Corporation) shall receive an annual fee of $25,000. The Chairman (not otherwise employed full-time by the Corporation or compensated for providing substantial consulting services to the Corporation) shall receive an annual fee of $150,000.

2. Directors (not otherwise employed full-time by the Corporation or compensated for providing substantial consulting services to the Corporation) serving as Chairman of a Committee of the Board shall receive an additional annual fee of $5,000.

   Commencing January 2002, Directors (not otherwise employed full-time by the Corporation or compensated for providing substantial consulting services to the Corporation) serving as Chairman of a Committee of the Board shall receive an additional annual fee of $10,000.

3. Directors not employed on a full-time basis by the Corporation shall receive as of each February 15th a non-qualified stock option to purchase 30,000 (the Chairman 60,000) shares of common stock at a per share exercise price equal to the then fair market value: provided that such Directors serving only a portion of the year shall receive a pro-rated portion thereof. Upon first joining the Board, Directors shall receive a non-qualified stock option to purchase 50,000 shares of common stock at a per share exercise price equal to the then fair market value.

BOARD POLICY - 02

COMPOSITION AND DUTIES OF

NOMINATING AND CORPORATE GOVERNANCE COMMITTEE

It is the policy of this Corporation to have a Nominating and Corporate Governance Committee to function on behalf of the Board of Directors with certain responsibilities as granted by the Board of Directors:

Composition:

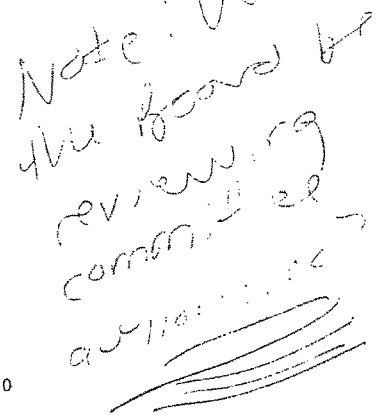
- Members of the Nominating and Corporate Governance Committee shall be elected for a one (1) year term.

- The Nominating and Corporate Governance Committee is currently composed of the following members:

  David M. Kies, Chairman
  Paul B. Kopperl
  William R. Miller

Duties

- The Nominating and Corporate Governance Committee considers and makes recommendations to the Board regarding Board and committee nominees and membership, director performance and officer candidates. The Nominating and Corporate Governance Committee also considers and makes recommendations to the Board with respect to corporate organizational and governance matters.



BOARD POLICY - 03

COMPOSITION AND DUTIES OF THE EXECUTIVE COMMITTEE

It is the policy of this Corporation to have an Executive Committee to function on behalf of the Board of Directors with certain responsibilities as granted by the Board of Directors:

Composition

- Members of the Executive Committee shall be elected for a one (1) year term. The Chief Executive Officer of the Corporation shall be a permanent member of the Executive Committee.

- The Executive Committee is currently composed of the following members:

  Samuel D. Waksal, Chairman
  Robert F. Goldhammer
  Harlan W. Waksal

Duties

- The Executive Committee acts for the Board of Directors when formal Board action is required between Board meetings. The Executive Committee has all the authority of the Board in the management of the business and affairs of the Company, except those powers that by law or pursuant to the Company's By-laws cannot be delegated by the Board of Directors.

BOARD POLICY - 04

COMPOSITION AND DUTIES OF THE

COMPENSATION & STOCK OPTION COMMITTEE

It is the policy of this Corporation to have a Compensation & Stock Option Committee to function on behalf of the Board of Directors with certain responsibilities as granted by the Board of Directors:

Composition

- The Compensation & Stock Option Committee shall consist of at least two (2) outside Directors who have been selected to serve on the Committee, one (1) of whom shall be designated chairman.

- Members of the Compensation & Stock Option Committee shall be elected for one (1) year terms.

- The Compensation and Stock Options Committee is currently composed of the following members:

  Robert F. Goldhammer, Chairman
  Richard Barth
  David M. Kies
  Paul B. Kopperl

- The Compensation and Stock Option Committee also has a subcommittee composed of Richard Barth, David M. Kies and Paul B. Kopperl. The subcommittee has the authority of the full committee. It was formed for the purpose of ensuring the ability to make option grants exempt from the short swing trading liability under Section 16(b) of the Exchange Act.

Duties

- The Compensation and Stock Option Committee is responsible for developing executive compensation policies. The Compensation and Stock Option Committee (i) determines on an annual basis the base salary to be paid to the Chief Executive Officer and determines bonuses and incentive awards to be paid from time to time to the Chief Executive Officer; and (ii) approves on an annual basis a salary plan for other senior officers on the recommendation of the Chief Executive Officer in conjunction with other senior personnel and approves bonuses and incentive awards to be paid from time to time to such senior officers on the recommendation of the Chief Executive Officer in conjunction with other senior personnel. The Compensation and Stock Option Committee also administers the Company's various stock option plans, including the granting of options thereunder. Management is responsible for the granting of options under and in accordance with the Company's option plans to new employees and employees, in accordance with parameters established by the Board of Directors.

BOARD POLICY - 05

COMPOSITION AND DUTIES OF THE

AUDIT COMMITTEE

It is the policy of this Corporation to have an Audit Committee to function on behalf of the Board of Directors with certain responsibilities as granted by the Board of Directors:

Composition

- Members of the Audit Committee shall be elected for a one (1) year term.
- The Audit Committee is currently composed of the following members:

  Paul B. Kopperl, Chairman
  Richard Barth
  William R. Miller

Following is the Charter of the Audit Committee:

I. Committee Purpose

The Audit Committee is appointed by the Board of Directors to assist the Board in fulfilling its oversight responsibilities. The Audit Committee's primary duties and responsibilities are to:

- Monitor the integrity of the Company's financial reporting process and systems of internal controls regarding finance, accounting, and legal compliance.
- Monitor the independence and performance of the Company's independent auditors.
- Provide an avenue of communication among the independent auditors, management, and the Board of Directors.

The Audit Committee has the authority to conduct any investigation appropriate to fulfilling its responsibilities, and it has direct access to the independent auditors as well as anyone in the organization. The Audit Committee has the ability to retain, at the Company's expense, special legal, accounting, or other consultants or experts it deems necessary in the performance of its duties.

II. Audit Committee Composition and Meetings

Audit Committee members shall meet the requirements of the NASD. The Audit Committee shall be comprised of three or more directors as determined by the Board, each of whom shall be independent nonexecutive directors, free from any relationship that would interfere with the exercise of his or her independent judgment. All members of the Committee shall have a basic understanding of finance and accounting and be able to read and understand fundamental financial statements, and at least one member of the Committee shall have accounting or related financial management expertise.

Audit Committee members shall be appointed by the Board. If an audit committee Chair is not designated or present, the members of the Committee may designate a Chair by majority vote of the Committee membership.

The Committee shall meet approximately three times annually, or more frequently as circumstances dictate. The Audit Committee Chair shall prepare and/or approve an agenda in advance of each meeting. The Committee should meet privately in executive session at least annually with management, the independent auditors, and as a committee to discuss any matters that the Committee or each of these groups believe should be discussed. In addition, the Committee, or at least its Chair, should communicate with management and the independent auditors quarterly to review the Company's financial statements and significant findings based upon the auditors' review procedures.

III. Audit Committee Responsibilities and Duties

Review Procedures

1. Review and reassess the adequacy of this Charter at least annually. Submit the Charter to the Board of Directors for approval and have the document published in accordance with SEC regulations.

2. Review the Company's annual audited financial statements prior to filing or distribution. Review should include discussion with management and independent auditors of significant issues regarding accounting principles, practices, and judgments.

3. In consultation with management and the independent auditors, consider the integrity of the Company's financial reporting processes and controls. Discuss significant financial risk exposures and the steps management has taken to monitor, control, and report such exposures. Review significant findings prepared by the independent auditors together with management's responses.

4. Review with financial management and the independent auditors the Company's quarterly financial results prior to the release of earnings and/or the Company's quarterly financial statements prior to filing or distribution. Discuss any significant changes to the Company's accounting principles and any items required to be communicated by the independent auditors in accordance with SAS 61. The Chair of the Committee may represent the entire Audit Committee for purposes of this review.

5. Periodically perform self-assessment of Audit Committee performance.

6. Annually review policies and procedures as well as test results associated with directors' and officers' expense accounts and perquisites. Annually review a summary of directors' and officers' related party transactions and potential conflicts of interest.

Independent Auditors

7. The independent auditors are ultimately accountable to the Audit Committee and the Board of Directors. The Audit Committee shall review the independence and performance of the auditors and annually recommend to the Board of Directors the appointment of the independent auditors or approve any discharge of auditors when circumstances warrant.

8. On an annual basis, the Committee should review and discuss with the independent auditors all significant relationships they have with the Company that could impair the auditors' independence.

9. Review the independent auditors audit plan – discuss scope, staffing, locations, reliance upon management, and general audit approach.

10. Prior to releasing the year-end earnings, discuss the results of the audit with the independent auditors. Discuss certain matters required to be communicated to audit committees in accordance with AICPA SAS 61.

11. Consider the independent auditors' judgments about the quality and appropriateness of the Company's accounting principles as applied in its financial reporting.

Legal Compliance

12. On at least an annual basis, review with the Company's counsel, any legal matters that could have a significant impact on the organization's financial statements, the Company's compliance with applicable laws and regulations, and inquiries received from regulators or governmental agencies.

Other Audit Committee Responsibilities

13. Annually prepare a report to shareholders as required by the Securities and Exchange Commission. The report should be included in the Company's annual proxy statement.

14. Perform any other activities consistent with this Charter, the Company's by-laws, and governing law, as the Committee or the Board deems necessary or appropriate.

15. Maintain minutes of meetings and periodically report to the Board of Directors on significant results of the foregoing activities.

BOARD POLICY - 06

COMPOSITION AND DUTIES OF

RESEARCH OVERSIGHT COMMITTEE

It is the policy of this Corporation to have a Research Oversight Committee to function on behalf of the Board of Directors with certain responsibilities as granted by the Board of Directors:

Composition:

- Members of the Research Oversight Committee shall be elected for a one (1) year term.
- The Research Oversight Committee is currently composed of the following members:

  Samuel D. Waksal, Chairman
  Vincent T. DeVita, Jr.
  John Mendelsohn
  Harlan W. Waksal
  Arnold Levine

Duties

- The Research Oversight Committee considers and makes recommendations to the Board regarding the direction of the research focus of the Company.

BOARD POLICY - 07

FILLING VACANCIES ON THE

BOARD OF DIRECTORS

Pursuant to the Company's By-laws, vacancies which may occur on the Company's Board of Directors may be filled by a majority of the Directors then in office, although less than a quorum, or by the sole remaining Director. Any Director elected or appointed to fill a vacancy shall hold office until the next annual meeting of the stockholders and his or her successor is elected and qualified or until his or her earlier resignation or removal. The Nominating and Corporate Governance Committee considers and make recommendations to the Board regarding Board and committee nominees.

BOARD POLICY - 08

FILLING VACANCIES ON COMMITTEES

OF THE BOARD OF DIRECTORS

When a vacancy occurs on any committee of the Board, the Chief Executive Officer shall review the opening with present committee members and members of the Nominating and Corporate Governance Committee. Based upon the conclusions of such a review, the Chief Executive Officer shall contact the members of the Board, other than the individual selected, to determine if he would be acceptable for appointment to such position. If a majority of the Board agrees, the Chief Executive Officer will contact such individual to determine if he would be willing to undertake such additional responsibility. If he is, the matter of his appointment will be placed on the agenda at the next meeting of the Board of Directors.

BOARD POLICY -09

INSIDER TRADING POLICY

INSIDER TRADING POLICY

Background:

I. General Rule

The U.S. securities laws regulate the purchase and sale of securities in the interest of protecting the investing public. U.S. securities laws give the Company, its directors, officers and other employees, among others, the responsibility to ensure that information about the Company is not used unlawfully in the purchase and sale of securities.

All directors, officers and other employees should pay close attention to the laws against trading on "inside" information. These laws are based upon the belief that all persons trading in a company's securities should have equal access to all "material" information about the company. For example, if an employee of a company knows material, non-public information, that employee is prohibited from buying or selling stock in the company until the information has been disclosed to the public. That is because the employee knows information that will very likely cause the stock price to change, and it would be unfair for the employee to have an advantage that the rest of the investing public does not have. In fact, it is more than unfair, it is fraudulent and illegal. Civil and criminal penalties for this kind of activity are severe.

The general rule is that it is a violation of the federal securities laws for any person to buy or sell securities if he or she is in possession of material inside information. Information is "material" if it could affect a person's decision whether to buy, sell or hold the securities. It is "inside" information if it has not been publicly disclosed. Furthermore, it is illegal for any person in possession of a material inside information to provide other people with such information or to recommend that they buy or sell the securities ("tipping"). In that case, they may both be held liable.

The Securities and Exchange Commission, the stock exchanges (including NASDAQ), and plaintiffs' lawyers focus on uncovering apparent insider trading. A breach of the insider trading laws could expose the insider to criminal fines of the greater of $1,000,000 or three times the profits earned or losses avoided and imprisonment up to ten years, in addition to civil penalties (up to three times the profits earned or losses avoided) and injunctive actions. In addition, punitive damages may be imposed under state laws.

Securities laws also subject "controlling persons" to civil penalties for illegal insider trading by employees. "Controlling Persons" include the company, and is being interpreted by the SEC to include directors, officers, and supervisors. These persons may be subject to fines up to the greater of $1,000,000 or three times the profits earned (or losses avoided) by the insider trader.

II. To Whom Does this Policy Apply?

The prohibition against trading on material inside information applies to directors, officers, and all other employees, and to other people who gain access to that information.

III. Other Companies' Securities

The same rules apply to securities of other companies. Employees who learn material information about suppliers, customers, or competitors through their work at the Company, should keep it confidential and not buy or sell securities in such companies until the information becomes public. Employees should not give tips about such securities.

IV. Policy

The following policy should be followed in order to ensure compliance with applicable anti-fraud laws and with the Company's policies.

A. Trading in Company Securities - Generally

No director, officer or employee should place a purchase or sale order, or recommend that another person place a purchase or sale order, in the Company's securities when he or she has knowledge of material information concerning the Company that has not been disclosed to the public. The exercise of stock options (without immediate sale) is not subject to this policy. However, stock that was acquired upon exercise of a stock option will be treated like any other stock, and may not be sold by a director, officer or employee who is in possession of material inside information. After material non-public information has been publicly released, any director, officer or employee who possessed the material non-public information should allow to elapse, before such director, officer or employee trades, a minimum of four hours during which trading on The Nasdaq Stock Market is underway.

All ImClone directors and officers must receive authorization from ImClone's Office of the General Counsel prior to executing any transaction in ImClone stock. (Contact John B. Landes or Catherine M. Vaczy at (212) 645-1405).

B. Trading in Standardized Options

The Company's put and call options are publicly traded. Employees should not trade in such standardized options, or recommend that another person so trade, when he or she has knowledge of material information concerning the Company that has not been disclosed to the public. Further, the Company believes that the trading by officers and directors in the Company's standardized options is inappropriate because it gives the appearance that officers and directors are engaging in short term speculation in the Company's stock. Accordingly, it is the Company's policy that officers and directors not engage in transactions in the Company's standardized options.

C. Trading in Other Securities

No director, officer or employee should place a purchase or sale order, or recommend that another person place a purchase or sale order, in the securities of another corporation if the employee learns in the course of his or her employment or tenure, confidential information about the other corporation that is likely to affect the value of those securities. For example, it would be a violation of the securities laws if an individual learned through Company sources that the Company intended to purchase assets from a company and then bought or sold stock in that other company because of the likely increase or decrease in the value of its securities.

D. Black-out Periods

There will be periods of time when it is clear that material non-public information is known by several employees, officers and directors of the Company. An example would be the making of a seminal discovery in the Company's science, or significant results in one of its clinical trials, or the pending announcement of an important strategic alliance for the Company. In such cases, the Company may determine that stock transactions in the Company's stock by employees, officers or directors must be prohibited and therefore there would be a "Blackout" period during which no such trading could take place.

E. Prior Arrangements Relating to Purchase and Sale

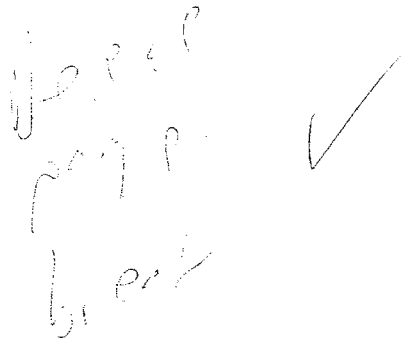
The Company in its sole discretion may agree to an employee, officer or director entering into an arrangement relating to the purchase or sale of securities of the Company under circumstances where the individual has no control over the timing of the transaction. If such an arrangement is established, and such individual entered into the arrangement with the prior approval of the Company and when such individual was not aware of material, non-public information, the individual may purchase or sell securities pursuant to such arrangement without regard to whether they were aware of material, non-public information and without requiring prior approval of such transaction and without regard to any "Blackout". Specifically, such individual may purchase or sell securities pursuant to a binding contract or plan, or irrevocable instructions to purchase or sell securities on a future date, if the following conditions are met:

- The individual was not aware of material, non-public information when such individual entered into a binding contract to purchase or sell the security, provided written instructions to another person to execute the trade for such person's account, or adopted a written plan for trading securities.

- The contract, instructions or plan (1) expressly specifies the amount and price of the securities to be bought or sold and the date of the transaction; (2) provides a written formula or algorithm, or computer program, for determining the amount, price, and date for the transaction; or (3) does not permit the officer, director or employee to exercise any subsequent influence over how, when, or whether to effect purchases or sales; provided, in addition, that any other person who did exercise such influence was not aware of material non-public information when doing so.

- The purchase or sale that occurs is pursuant to the prior contract, instruction or plan. A purchase or sale is not pursuant to a contract, instruction, or plan if, among other things, the officer, director or employee altered or deviated from the contract, instruction, or plan or entered into or altered a

corresponding or hedging transaction or position with respect to those securities, or the contract, instruction, or plan to purchase or sell securities was not given or entered into in good faith or as a part of a plan or scheme to evade the prohibition on insider trading.



F. Communication of Officer or Director Trading

To assure that there are no surprises within the Company that might arise from a reported transaction of Company stock unknown to the officers of the Company, the Company has made it a policy that all transactions of Company stock by executive officers and directors be reported by the General Counsel's Office promptly to the following: CEO, COO, CFO and Department of Investor Relation.

G. Nondisclosure/No Comment Policy

Material inside information must not be disclosed to anyone, except to persons with the Company whose positions require them to know it, until it has been publicly released by the Company.

In addition, ImClone has adopted the following no-comment policy.

It is a policy of this Company that directors, officers, employees and representatives of the Company are prohibited from commenting on or responding to inquiries or rumors concerning material prospective developments or transactions involving the Company; that all directors, officers, employees and representatives of the Company are hereby directed to respond to any such inquiry or rumor only with a statement to the effect that it is the policy of the Company not to comment on or respond to inquiries or rumors concerning prospective corporate developments or transactions; and that no information with respect to a prospective development or transaction shall be provided to any member of the media, investment community or general public by any director, officer, employee or representative of the Company until such time as the Company has made a formal public announcement of the corporate development or transaction. The Company has an employee whose role it is to interact with those who would seek information about the Company, including Shareholders, and that is Andrea Rabney, the Company's Vice President of Corporate Development and Investor Relations. The best policy when such inquiries are directed to you is to refer them directly to Andrea.

H. Questions

Any questions regarding this Policy, its interpretation and effect should be referred to John B. Landes or Catherine M. Vaczy.

RESTATED BY-LAWS

OF

IMCLONE SYSTEMS INCORPORATED

ARTICLE I

Stockholders

Section 1.1. Annual Meetings. An annual meeting of stockholders shall be held for the election of directors at such date, time and place either within or without the State of Delaware as may be designated by the Board of Directors from time to time. Any other proper business may be transacted at the annual meeting.

Section 1.2. Special Meetings. Special meetings of stockholders may be called at any time by the Chairman of the Board, if any, the Vice Chairman of the Board, if any, the President or the Board of Directors, to be held at such date, time and place either within or without the State of Delaware as may be stated in the notice of the meeting.

Section 1.3. Notice of Meetings. Whenever stockholders are required or permitted to take any action at a meeting, a written notice of the meeting shall be given which shall state the place, date and hour of the meeting, and, in the case of a special meeting, the purpose or purposes for which the meeting is called. Unless otherwise provided by law, the written notice of any meeting shall be given not less than ten nor more than sixty days before the date of the meeting to each stockholder entitled to vote at such meeting. If mailed, such notice shall be deemed to be given when deposited in the United States mail, postage prepaid, directed to the stockholder at such stockholder's address as it appears on the records of the Corporation.

Section 1.4. Adjournments. Any meeting of stockholders, annual or special, may be adjourned from time to time, to reconvene at the same or some other place, and notice need not be given of any such adjourned meeting if the time and place thereof are announced at the meeting at which the adjournment is taken. At the adjourned meeting the Corporation may transact any business which might have been transacted at the original meeting. If the adjournment is for more than thirty days, or if after the adjournment a new record date is fixed for the adjourned meeting, a notice of the adjourned meeting shall be given to each stockholder of record entitled to vote at the meeting.

Section 1.5. Quorum. At each meeting of stockholders, except where otherwise provided by law or the certificate of incorporation or these by-laws, the holders of a majority of the outstanding shares of stock entitled to vote on a matter at the meeting, present in person or represented by proxy, shall constitute a quorum. In the absence of a quorum of the holders of any class of stock entitled to vote on a matter, the holders of such class so present or represented may, by majority vote, adjourn the meeting of such class from time to time in the manner provided by Section 1.4 of these by-laws until a quorum of such class shall be so present or represented. Shares of its own capital stock

belonging on the record date for the meeting to the Corporation or to another corporation, if a majority of the shares entitled to vote in the election of directors of such other corporation is held, directly or indirectly, by the Corporation, shall neither be entitled to vote nor be counted for quorum purposes; provided, however, that the foregoing shall not limit the right of the Corporation to vote stock, including but not limited to its own stock, held by it in a fiduciary capacity.

Section 1.6. Organization. Meetings of stockholders shall be presided over by the Chairman of the Board, if any, or in the absence of the Chairman of the Board by the President, or in the absence of the foregoing persons by a chairman designated by the Board of Directors, or in the absence of such designation by a chairman chosen at the meeting. The Secretary, or in the absence of the Secretary an Assistant Secretary, shall act as secretary of the meeting, but in the absence of the Secretary and any Assistant Secretary the chairman of the meeting may appoint any person to act as secretary of the meeting.

The order of business at each such meeting shall be as determined by the chairman of the meeting. The chairman of the meeting shall have the right and authority to prescribe such rules, regulations and procedures and to do all such acts and things as are necessary or desirable for the proper conduct of the meeting, including, without limitation, the establishment of procedures for the maintenance of order and safety, limitations on the time allotted to questions or comments on the affairs of the Corporation, restrictions on entry to such meeting after the time prescribed for the commencement thereof and the opening and closing of the voting polls.

Section 1.7. Inspectors. Prior to any meeting of stockholders, the Board of Directors or the President shall appoint one or more inspectors to act at such meeting and make a written report thereof and may designate one or more persons as alternate inspectors to replace any inspector who fails to act. If no inspector or alternate is able to act at the meeting of stockholders, the person presiding at the meeting shall appoint one or more inspectors to act at the meeting. Each inspector, before entering upon the discharge of his or her duties, shall take and sign an oath faithfully to execute the duties of inspector with strict impartiality and according to the best of his or her ability. The inspectors shall ascertain the number of shares outstanding and the voting power of each, determine the shares represented at the meeting and the validity of proxies and ballots, count all votes and ballots, determine and retain for a reasonable period a record of the disposition of any challenges made to any determination by the inspectors and certify their determination of the number of shares represented at the meeting and their count of all votes and ballots. The inspectors may appoint or retain other persons to assist them in the performance of their duties. The date and time of the opening and closing of the polls for each matter upon which the stockholders will vote at a meeting shall be announced at the meeting. No ballot, proxy or vote, nor any revocation thereof or change thereto, shall be accepted by the inspectors after the closing of the polls. In determining the validity and counting of proxies and ballots, the inspectors shall be limited to an examination of the proxies, any envelopes submitted therewith, any information provided by a stockholder who submits a proxy by telegram, cablegram or other electronic transmission from which it can be determined that the proxy was authorized by the stockholder, ballots and the regular books and records of the corporation, and they may also consider other reliable information for the limited purpose of reconciling proxies and ballots submitted by or on behalf of banks, brokers, their nominees or similar persons which represent more votes than the holder of a proxy is authorized by the record owner to cast or more votes than the stockholder holds of record. If the inspectors consider other reliable information for such purpose, they shall, at the time they make their certification, specify the precise information considered by them, including the person or persons from whom they obtained the information, when the information

was obtained, the means by which the information was obtained and the basis for the inspectors' belief that such information is accurate and reliable.

Section 1.8. Voting; Proxies. Unless otherwise provided in the certificate of incorporation, each stockholder entitled to vote at any meeting of stockholders shall be entitled to one vote for each share of stock held by such stockholder which has voting power upon the matter in question. Each stockholder entitled to vote at a meeting of stockholders or to express consent or dissent to corporate action in writing without a meeting may authorize another person or persons to act for such stockholder by proxy, but no such proxy shall be voted or acted upon after three years from its date, unless the proxy provides for a longer period. A duly executed proxy shall be irrevocable if it states that it is irrevocable and if, and only as long as, it is coupled with an interest sufficient in law to support an irrevocable power, regardless of whether the interest with which it is coupled is an interest in the stock itself or an interest in the Corporation generally. A stockholder may revoke any proxy which is not irrevocable by attending the meeting and voting in person or by filing an instrument in writing revoking the proxy or another duly executed proxy bearing a later date with the Secretary of the Corporation. Voting at meetings of stockholders need not be by written ballot and need not be conducted by inspectors unless the holders of a majority of the outstanding shares of all classes of stock entitled to vote thereon present in person or represented by proxy at such meeting shall so determine. Directors shall be elected by a plurality of the votes of the shares present in person or represented by proxy at the meeting and entitled to vote on the election of directors. In all other matters, unless otherwise provided by law or by the certificate of incorporation or these by-laws, the affirmative vote of the holders of a majority of the shares present in person or represented by proxy at the meeting and entitled to vote on the subject matter shall be the act of the stockholders. Where a separate vote by class or classes is required, the affirmative vote of the holders of a majority of the shares of such class or classes present in person or represented by proxy at the meeting shall be the act of such class or classes, except as otherwise provided by law or by the certificate of incorporation or these by-laws.

Section 1.9. Fixing Date for Determination of Stockholders of Record. In order that the Corporation may determine the stockholders entitled to notice of or to vote at any meeting of stockholders or any adjournment thereof, the Board of Directors may fix a record date, which record date shall not precede the date upon which the resolution fixing the record date is adopted by the Board of Directors, and which record date shall not be more than sixty nor less than ten days before the date of such meeting. If no record date is fixed by the Board of Directors, the record date for determining stockholders entitled to notice of or to vote at a meeting of stockholders shall be at the close of business on the day next preceding the day on which notice is given, or, if notice is waived, at the close of business on the day next preceding the day on which the meeting is held. A determination of stockholders of record entitled to notice of or to vote at a meeting of stockholders shall apply to any adjournment of the meeting; provided, however, that the Board of Directors may fix a new record date for the adjourned meeting.

In order that the Corporation may determine the stockholders entitled to consent to corporate action in writing without a meeting, the Board of Directors may fix a record date, which record date shall not precede the date upon which the resolution fixing the record date is adopted by the Board of Directors, and which date shall not be more than ten days after the date upon which the resolution fixing the record date is adopted by the Board of Directors. If no record date has been fixed by the Board of Directors, the record date for determining stockholders entitled to consent to corporate action in writing without a meeting, when no prior action by the Board of Directors is required by law,

shall be the first date on which a signed written consent setting forth the action taken or proposed to be taken is delivered to the Corporation by delivery to its registered office in the State of Delaware, its principal place of business, or an officer or agent of the Corporation having custody of the book in which proceedings of meetings of stockholders are recorded. Delivery made to the Corporation's registered office shall be by hand or by certified or registered mail, return receipt requested. If no record date has been fixed by the Board of Directors and prior action by the Board of Directors is required by law, the record date for determining stockholders entitled to consent to corporate action in writing without a meeting shall be at the close of business on the day on which the Board of Directors adopts the resolution taking such prior action.

In order that the Corporation may determine the stockholders entitled to receive payment of any dividend or other distribution or allotment of any rights or the stockholders entitled to exercise any rights in respect of any change, conversion or exchange of stock, or for the purpose of any other lawful action, the Board of Directors may fix a record date, which record date shall not precede the date upon which the resolution fixing the record date is adopted, and which record date shall be not more than sixty days prior to such action. If no record date is fixed, the record date for determining stockholders for any such purpose shall be at the close of business on the day on which the Board of Directors adopts the resolution relating thereto.

Section 1.10. List of Stockholders Entitled to Vote. The Secretary shall prepare and make, at least ten days before every meeting of stockholders, a complete list of the stockholders entitled to vote at the meeting, arranged in alphabetical order, and showing the address of each stockholder and the number of shares registered in the name of each stockholder. Such list shall be open to the examination of any stockholder, for any purpose germane to the meeting, during ordinary business hours, for a period of at least ten days prior to the meeting, either at a place within the city where the meeting is to be held, which place shall be specified in the notice of the meeting, or, if not so specified, at the place where the meeting is to be held. The list shall also be produced and kept at the time and place of the meeting during the whole time thereof and may be inspected by any stockholder who is present.

Section 1.11. Consent of Stockholders in Lieu of Meeting. Unless otherwise provided in the certificate of incorporation or by law, any action required by law to be taken at any annual or special meeting of stockholders of the Corporation, or any action which may be taken at any annual or special meeting of such stockholders, may be taken without a meeting, without prior notice and without a vote, if a consent or consents in writing, setting forth the action so taken, shall be signed by the holders of outstanding stock having not less than the minimum number of votes that would be necessary to authorize or take such action at a meeting at which all shares entitled to vote thereon were present and voted and shall be delivered to the Corporation by delivery to (a) its registered office in the State of Delaware by hand or by certified mail or registered mail, return receipt requested, (b) its principal place of business, or (c) an officer or agent of the Corporation having custody of the book in which proceedings of meetings of stockholders are recorded. Every written consent shall bear the date of signature of each stockholder who signs the consent and no written consent shall be effective to take the corporate action referred to therein unless, within sixty days of the earliest dated consent delivered in the manner required by this by-law to the Corporation, written consents signed by a sufficient number of holders to take action are delivered to the Corporation by delivery to (a) its registered office in the State of Delaware by hand or by certified or registered mail, return receipt requested, (b) its principal place of business, or (c) an officer or agent of the Corporation having custody of the book in which proceedings of meetings of stockholders are recorded. Prompt notice of the taking of the

corporate action without a meeting by less than unanimous written consent shall be given to those stockholders who have not consented in writing and who, if the action had been taken at a meeting, would have been entitled to notice of the meeting if the record date for such meeting had been the date that written consents signed by a sufficient number of stockholders to take the action were delivered to the Corporation as provided in this Section 1.11.

Section 1.12. Advance Notice of Stockholder Proposals. At any annual or special meeting of stockholders, proposals by stockholders and persons nominated for election as directors by stockholders shall be considered only if advance notice thereof has been timely given as provided herein and such proposals or nominations are otherwise proper for consideration under applicable law and the certificate of incorporation and by-laws of the Corporation. Notice of any proposal to be presented by any stockholder or of the name of any person to be nominated by any stockholder for election as a director of the Corporation at any meeting of stockholders shall be delivered to the Secretary of the Corporation at its principal executive office not less than 60 nor more than 90 days prior to the date of the meeting; provided, however, that if the date of the meeting is first publicly announced or disclosed (in a public filing or otherwise) less than 70 days prior to the date of the meeting, such advance notice shall be given not more than ten days after such date is first so announced or disclosed. Public notice shall be deemed to have been given more than 70 days in advance of the annual meeting if the Corporation shall have previously disclosed, in these by-laws or otherwise, that the annual meeting in each year is to be held on a determinable date, unless and until the Board determines to hold the meeting on a different date. Any stockholder who gives notice of any such proposal shall deliver therewith the text of the proposal to be presented and a brief written statement of the reasons why such stockholder favors the proposal and setting forth such stockholder's name and address, the number and class of all shares of each class of stock of the Corporation beneficially owned by such stockholder and any material interest of such stockholder in the proposal (other than as a stockholder). Any stockholder desiring to nominate any person for election as a director of the Corporation shall deliver with such notice a statement in writing setting forth the name of the person to be nominated, the number and class of all shares of each class of stock of the Corporation beneficially owned by such person, the information regarding such person required by paragraphs (a), (e) and (f) of Item 401 of Regulation S-K adopted by the Securities and Exchange Commission (or the corresponding provisions of any regulation subsequently adopted by the Securities and Exchange Commission applicable to the Corporation), such person's signed consent to serve as a director of the Corporation if elected, such stockholder's name and address and the number and class of all shares of each class of stock of the Corporation beneficially owned by such stockholder. As used herein, shares "beneficially owned" shall mean all shares as to which such person, together with such person's affiliates and associates (as defined in Rule 12b-2 under the Securities Exchange Act of 1934), may be deemed to beneficially own pursuant to Rules 13d-3 and 13d-5 under the Securities Exchange Act of 1934, as well as all shares as to which such person, together with such person's affiliates and associates, has the right to become the beneficial owner pursuant to any agreement or understanding, or upon the exercise of warrants, options or rights to convert or exchange (whether such rights are exercisable immediately or only after the passage of time or the occurrence of conditions). The person presiding at the meeting, in addition to making any other determinations that may be appropriate to the conduct of the meeting, shall determine whether such notice has been duly given and shall direct that proposals and nominees not be considered if such notice has not been given.

ARTICLE II

Board of Directors

Section 2.1. Powers; Number; Qualifications. The business and affairs of the Corporation shall be managed by or under the direction of the Board of Directors, except as may be otherwise provided by law or in the certificate of incorporation. The Board of Directors shall consist of one or more members, the number thereof to be determined from time to time by the Board. Directors need not be stockholders.

Section 2.2. Election; Term of Office; Resignation; Removal; Vacancies. Each director shall hold office until his or her successor is elected and qualified or until his or her earlier resignation or removal. Any director may resign at any time upon written notice to the Board of Directors or to the President or the Secretary of the Corporation. Such resignation shall take effect at the time specified therein, and unless otherwise specified therein no acceptance of such resignation shall be necessary to make it effective. Any director or the entire Board of Directors may be removed, with cause, by the holders of a majority of the shares then entitled to vote at an election of directors. Unless otherwise provided in the certificate of incorporation or these by-laws, vacancies and newly created directorships resulting from any increase in the authorized number of directors elected by all of the stockholders having the right to vote as a single class or from any other cause may be filled by a majority of the directors then in office, although less than a quorum, or by the sole remaining director. Any director elected or appointed to fill a vacancy shall hold office until the next annual meeting of the stockholders and his or her successor is elected and qualified or until his or her earlier resignation or removal.

Section 2.3. Regular Meetings. Regular meetings of the Board of Directors may be held at such places within or without the State of Delaware and at such times as the Board may from time to time determine, and if so determined notice thereof need not be given.

Section 2.4. Special Meetings. Special meetings of the Board of Directors may be held at any time or place within or without the State of Delaware whenever called by the Chairman of the Board, by the President or by any two directors. Reasonable notice thereof shall be given by the person or persons calling the meeting.

Section 2.5. Participation in Meetings by Conference Telephone Permitted. Unless otherwise restricted by the certificate of incorporation or these by-laws, members of the Board of Directors, or any committee designated by the Board, may participate in a meeting of the Board or of such committee, as the case may be, by means of conference telephone or similar communications equipment by means of which all persons participating in the meeting can hear each other, and participation in a meeting pursuant to this by-law shall constitute presence in person at such meeting.

Section 2.6. Quorum; Vote Required for Action. At all meetings of the Board of Directors one-third of the entire Board shall constitute a quorum for the transaction of business. The vote of a majority of the directors present at a meeting at which a quorum is present shall be the act of the Board unless the certificate of incorporation or these by-laws shall require a vote of a greater number. In case at any meeting of the Board a quorum shall not be present, the members of the Board present may adjourn the meeting from time to time until a quorum shall be present.

Section 2.7. Organization. Meetings of the Board of Directors shall be presided over by the Chairman of the Board, if any, or in the absence of the Chairman of the Board by the President, or in their absence by a chairman chosen at the meeting. The Secretary, or in the absence of the Secretary an Assistant Secretary, shall act as secretary of the meeting, but in the absence of the Secretary and any Assistant Secretary the chairman of the meeting may appoint any person to act as secretary of the meeting.

Section 2.8. Action by Directors Without a Meeting. Unless otherwise restricted by the certificate of incorporation or these by-laws, any action required or permitted to be taken at any meeting of the Board of Directors, or of any committee thereof, may be taken without a meeting if all members of the Board or of such committee, as the case may be, consent thereto in writing, and the writing or writings are filed with the minutes of proceedings of the Board or committee.

Section 2.9. Compensation of Directors. Unless otherwise restricted by the certificate of incorporation or these by-laws, the Board of Directors shall have the authority to fix the compensation of directors. Directors shall be entitled to receive stock of the corporation and warrants, options and other rights to purchase stock of the corporation for their services rendered to the corporation if so determined by the Board of Directors.

ARTICLE III

Committees

Section 3.1. Committees. The Board of Directors may designate one or more committees, each committee to consist of one or more of the directors of the Corporation. The Board may designate one or more directors as alternate members of any committee, who may replace any absent or disqualified member at any meeting of the committee. In the absence or disqualification of a member of a committee, the member or members thereof present at any meeting and not disqualified from voting, whether or not such member or members constitute a quorum, may unanimously appoint another member of the Board to act at the meeting in the place of any such absent or disqualified member. Any such committee, to the extent provided in the resolution of the Board of Directors or in these by-laws, shall have and may exercise all the powers and authority of the Board of Directors in the management of the business and affairs of the Corporation, and may authorize the seal of the Corporation to be affixed to all papers which may require it; but no such committee shall have the power or authority in reference to the following matters: (i) approving or adopting, or recommending to the stockholders, any action or matter expressly required by law to be submitted to stockholders for approval, (ii) adopting, amending or repealing these By-Laws or (iii) removing or indemnifying directors.

Section 3.2. Committee Rules. Unless the Board of Directors otherwise provides, each committee designated by the Board may adopt, amend and repeal rules for the conduct of its business. In the absence of a provision by the Board or a provision in the rules of such committee to the contrary, a majority of the entire authorized number of members of such committee shall constitute a quorum for the transaction of business, the vote of a majority of the members present at a meeting at the time of such vote if a quorum is then present shall be the act of such committee, and in other respects each committee shall conduct its business in the same manner as the Board conducts its business pursuant to Article II of these by-laws.

ARTICLE IV

Officers

Section 4.1. Officers; Election. As soon as practicable after the annual meeting of stockholders in each year, the Board of Directors shall elect a President and a Secretary, and it may, if it so determines, elect from among its members a Chairman of the Board. The Board may also elect one or more Vice Presidents, one or more Assistant Vice Presidents, one or more Assistant Secretaries, a Treasurer and one or more Assistant Treasurers and such other officers as the Board may deem desirable or appropriate and may give any of them such further designations or alternate titles as it considers desirable. Any number of offices may be held by the same person unless the certificate of incorporation or these by-laws otherwise provide.

Section 4.2. Term of Office; Resignation; Removal; Vacancies. Unless otherwise provided in the resolution of the Board of Directors electing any officer, each officer shall hold office until his or her successor is elected and qualified or until his or her earlier resignation or removal. Any officer may resign at any time upon written notice to the Board or to the President or the Secretary of the Corporation. Such resignation shall take effect at the time specified therein, and unless otherwise specified therein no acceptance of such resignation shall be necessary to make it effective. The Board may remove any officer with or without cause at any time. Any such removal shall be without prejudice to the contractual rights of such officer, if any, with the Corporation, but the election of an officer shall not of itself create contractual rights. Any vacancy occurring in any office of the Corporation by death, resignation, removal or otherwise may be filled by the Board at any regular or special meeting.

Section 4.3. Chairman of the Board. The Chairman of the Board, if any, shall preside at all meetings of the Board of Directors and of the stockholders at which he or she shall be present and shall have and may exercise such powers as may, from time to time, be assigned to him or her by the Board or as may be provided by law.

Section 4.4. President. In the absence of the Chairman of the Board, the President shall preside at all meetings of the Board of Directors and of the stockholders at which he or she shall be present. The President shall be the chief executive officer and shall have general charge and supervision of the business of the Corporation and, in general, shall perform all duties incident to the office of president of a corporation and such other duties as may, from time to time, be assigned to him or her by the Board or as may be provided by law.

Section 4.5. Vice Presidents. The Vice President or Vice Presidents, at the request or in the absence of the President or during the President's inability to act, shall perform the duties of the President, and when so acting shall have the powers of the President. If there be more than one Vice President, the Board of Directors may determine which one or more of the Vice Presidents shall perform any of such duties; or if such determination is not made by the Board, the President may make such determination; otherwise any of the Vice Presidents may perform any of such duties. The Vice President or Vice Presidents shall have such other powers and shall perform such other duties as may, from time to time, be assigned to him or her or them by the Board or the President or as may be provided by law.

Section 4.6. Secretary. The Secretary shall have the duty to record the proceedings of the meetings of the stockholders, the Board of Directors and any committees in a book to be kept for that purpose, shall see that all notices are duly given in accordance with the provisions of these by-laws or as required by law, shall be custodian of the records of the Corporation, may affix the corporate seal to any document the execution of which, on behalf of the Corporation, is duly authorized, and when so affixed may attest the same, and, in general, shall perform all duties incident to the office of secretary of a corporation and such other duties as may, from time to time, be assigned to him or her by the Board or the President or as may be provided by law.

Section 4.7. Treasurer. The Treasurer shall have charge of and be responsible for all funds, securities, receipts and disbursements of the Corporation and shall deposit or cause to be deposited, in the name of the Corporation, all moneys or other valuable effects in such banks, trust companies or other depositories as shall, from time to time, be selected by or under authority of the Board of Directors. If required by the Board, the Treasurer shall give a bond for the faithful discharge of his or her duties, with such surety or sureties as the Board may determine. The Treasurer shall keep or cause to be kept full and accurate records of all receipts and disbursements in books of the Corporation, shall render to the President and to the Board, whenever requested, an account of the financial condition of the Corporation, and, in general, shall perform all the duties incident to the office of treasurer of a corporation and such other duties as may, from time to time, be assigned to him or her by the Board or the President or as may be provided by law.

Section 4.8. Other Officers. The other officers, if any, of the Corporation shall have such powers and duties in the management of the Corporation as shall be stated in a resolution of the Board of Directors which is not inconsistent with these by-laws and, to the extent not so stated, as generally pertain to their respective offices, subject to the control of the Board. The Board may require any officer, agent or employee to give security for the faithful performance of his or her duties.

ARTICLE V

Stock

Section 5.1. Certificates. Every holder of stock in the Corporation shall be entitled to have a certificate signed by or in the name of the Corporation by the Chairman of the Board of Directors, if any, or the President or a Vice President, and by the Treasurer or an Assistant Treasurer, or the Secretary or an Assistant Secretary, of the Corporation, representing the number of shares of stock in the Corporation owned by such holder. If such certificate is manually signed by one officer or manually countersigned by a transfer agent or by a registrar, any other signature on the certificate may be a facsimile. In case any officer, transfer agent or registrar who has signed or whose facsimile signature has been placed upon a certificate shall have ceased to be such officer, transfer agent or registrar before such certificate is issued, it may be issued by the Corporation with the same effect as if such person were such officer, transfer agent or registrar at the date of issue.

Section 5.2. Lost, Stolen or Destroyed Stock Certificates; Issuance of New Certificates. The Corporation may issue a new certificate of stock in the place of any certificate theretofore issued by it, alleged to have been lost, stolen or destroyed, and the Corporation may require the owner of the lost, stolen or destroyed certificate, or such owner's legal representative, to give the Corporation a

bond sufficient to indemnify it against any claim that may be made against it on account of the alleged loss, theft or destruction of any such certificate or the issuance of such new certificate.

ARTICLE VI

Miscellaneous

Section 6.1. Fiscal Year. The fiscal year of the Corporation shall be January 1 to December 31 in each year.

Section 6.2. Seal. The Corporation may have a corporate seal which shall have the name of the Corporation inscribed thereon and shall be in such form as may be approved from time to time by the Board of Directors. The corporate seal may be used by causing it or a facsimile thereof to be impressed or affixed or in any other manner reproduced.

Section 6.3. Waiver of Notice of Meetings of Stockholders, Directors and Committees. Whenever notice is required to be given by law or under any provision of the certificate of incorporation or these by-laws, a written waiver thereof, signed by the person entitled to notice, whether before or after the time stated therein, shall be deemed equivalent to notice. Attendance of a person at a meeting shall constitute a waiver of notice of such meeting, except when the person attends a meeting for the express purpose of objecting, at the beginning of the meeting, to the transaction of any business because the meeting is not lawfully called or convened. Neither the business to be transacted at, nor the purpose of, any regular or special meeting of the stockholders, directors or members of a committee of directors need be specified in any written waiver of notice unless so required by the certificate of incorporation or these by-laws.

Section 6.4. Indemnification of Directors, Officers and Employees. The Corporation shall indemnify to the full extent permitted by law any person made or threatened to be made a party to any action, suit or proceeding, whether civil, criminal, administrative or investigative, by reason of the fact that such person or such person's testator or intestate is or was a director, officer or employee of the Corporation or serves or served at the request of the Corporation any other enterprise as a director, officer or employee. Expenses, including attorneys' fees, incurred by any such person in defending any such action, suit or proceeding shall be paid or reimbursed by the Corporation promptly upon receipt by it of an undertaking of such person to repay such expenses if it shall ultimately be determined that such person is not entitled to be indemnified by the Corporation. The rights provided to any person by this by-law shall be enforceable against the Corporation by such person who shall be presumed to have relied upon it in serving or continuing to serve as a director, officer or employee as provided above. No amendment of this by-law shall impair the rights of any person arising at any time with respect to events occurring prior to such amendment. For purposes of this by-law, the term "Corporation" shall include any predecessor of the Corporation and any constituent corporation (including any constituent of a constituent) absorbed by the Corporation in a consolidation or merger; the term "other enterprise" shall include any corporation, partnership, joint venture, trust or employee benefit plan; service "at the request of the Corporation" shall include service as a director, officer or employee of the Corporation which imposes duties on, or involves services by, such director, officer or employee with respect to an employee benefit plan, its participants or beneficiaries; any excise taxes assessed on a person with respect to an employee benefit plan shall be deemed to be indemnifiable expenses; and action by a person with respect to an employee benefit plan which such

person reasonably believes to be in the interest of the participants and beneficiaries of such plan shall be deemed to be action not opposed to the best interests of the Corporation.

Section 6.5. Interested Directors; Quorum. No contract or transaction between the Corporation and one or more of its directors or officers, or between the Corporation and any other corporation, partnership, association or other organization in which one or more of its directors or officers are directors or officers, or have a financial interest, shall be void or voidable solely for this reason, or solely because the director or officer is present at or participates in the meeting of the Board of Directors or committee thereof which authorizes the contract or transaction, or solely because his or her or their votes are counted for such purpose, if: (1) the material facts as to his or her relationship or interest and as to the contract or transaction are disclosed or are known to the Board or the committee, and the Board or committee in good faith authorizes the contract or transaction by the affirmative votes of a majority of the disinterested directors, even though the disinterested directors be less than a quorum; or (2) the material facts as to his or her relationship or interest and as to the contract or transaction are disclosed or are known to the stockholders entitled to vote thereon, and the contract or transaction is specifically approved in good faith by vote of the stockholders; or (3) the contract or transaction is fair as to the Corporation as of the time it is authorized, approved or ratified, by the Board, a committee thereof or the stockholders. Common or interested directors may be counted in determining the presence of a quorum at a meeting of the Board of Directors or of a committee which authorizes the contract or transaction.

Section 6.6. Form of Records. Any records maintained by the Corporation in the regular course of its business, including its stock ledger, books of account and minute books, may be kept on, or be in the form of, punch cards, magnetic tape, photographs, microphotographs or any other information storage device, provided that the records so kept can be converted into clearly legible form within a reasonable time. The Corporation shall so convert any records so kept upon the request of any person entitled to inspect the same.

Section 6.7. Amendment of By-Laws. These by-laws may be amended or repealed, and new by-laws adopted, by the Board of Directors, but the stockholders entitled to vote may adopt additional by-laws and may amend or repeal any by-law whether or not adopted by them.

SEC SECTION 16 REPORTING
And RULE 144

September 2001

To the Directors and Executive Officers
of ImClone Systems Incorporated

Re: Obligations Under the
Federal Securities Laws

The purpose of this letter is to provide you, a director and/or executive officer of ImClone Systems Incorporated (the "Company"), with a summary of those aspects of the United States securities laws that may apply to you. The Company's Common Stock (referred to herein as the "Common Stock" or the "equity securities") are subject to the periodic reporting requirements of the Securities Exchange Act of 1934 (the "1934 Act"). As a result, the Company must file certain periodic reports with the Securities and Exchange Commission (the "SEC") and comply with the SEC's proxy rules. In addition, as a director and/or an officer, you are subject to certain personal reporting requirements, to certain restrictions on your actions and to certain limitations on your right to trade in the Company's equity securities of the Company.

1. Form 4 and 5 Reports and Short-Swing Profits. Section 16(a) under the 1934 Act requires all directors and executive officers of the Company to report certain changes in beneficial ownership of the Company's equity securities to the SEC on Form 4 on a monthly basis and, with respect to certain transactions, on Form 5 on an annual basis. These filings serve as the backdrop for determining whether short-swing profits must be disgorged to the Company under the companion Section 16(b) under the 1934 Act.

In recent years, legislation and rule changes to enhance the Section 16(a) reporting requirements have increased the penalties and other adverse consequences for delinquent or inadequate filings. Moreover, the SEC has increased its efforts to police the revised reporting provisions, and has brought several enforcement actions for reporting violations.

In light of the regulatory developments in this area, management has adopted procedures to assist you in compliance with your reporting obligations under Section 16(a). These are spelled out in detail under Attachment 1. It is essential that you give these matters your careful attention. An updated summary of the short-swing profit provisions of Section 16(b) is contained in Attachment 2.

A miscalculation or misinterpretation of the applicable requirements under Section 16(b) can lead to significant adverse consequences. Accordingly, if you have any doubt as to the requirements, I urge you to consult your counsel or us and obtain specific advice based on the particular facts before you make any purchase or sale and before you otherwise change your position. Please note that if a transaction results in inadvertent liability, it may not be possible to avoid the liability simply by rescinding the transaction.

Please also note that the short-swing profit recapture provisions under Section 16(b) permit the matching of transactions occurring within six months of each other. Therefore, a sale (or purchase) may effectively preclude a purchase (or sale) within the following six months. Moreover, under certain circumstances, transactions that would not normally be deemed to be a purchase may be a "purchase" of the underlying Common Stock for purposes of Section 16(b). Consequently, considerable advance planning may be required at the time of any transaction, because a transaction can affect the ability to effect the opposite type of transaction for the following six months.

2. Short Sales. Under Section 16(c) of the 1934 Act, it is unlawful, with limited exceptions, for a director or an officer to sell any of the Company's equity securities that he does not own (i.e., to make a "short sale") or, if he sells equity securities that he does own, to fail to make delivery within twenty days after the sale or to deposit the equity securities in the mails within five days after the sale.

3. Insider Trading. The Company maintains a separate policy relating to Insider Trading, which is included in the Director's Handbook.

4. Limitation on Public Sales. Under the Securities Act of 1933, as amended (the "1933 Act"), sales of the Company's equity securities by persons who are either "controlling persons" of the Company or holders of "restricted securities" of the Company may be made only if there is an effective registration statement under the 1933 Act covering the securities to be sold, unless the sales are made in accordance with an available exemption. The principal applicable exemption is Rule 144, promulgated pursuant to the 1933 Act. I can advise you supplementally if some other exemption fits your particular facts.

"Restricted securities" are securities acquired in unregistered sales, directly or indirectly from the Company or from controlling persons of the Company or from other holders of restricted securities -- essentially securities acquired in a private placement. A "controlling person" is any person directly or indirectly controlling, controlled by or under common control with the Company. There is considerable uncertainty as to who is a controlling person (or "affiliate") for this purpose. In the interests of conservatism, and in view of the minimal practical limitations imposed by Rule 144, I recommend that all directors of the Company (including directors who are executive officers) comply with Rule 144 in making sales (directors other than directors who are executive officers may choose to include in their Forms 144 filed in connection with such sales a disclaimer that they are affiliates).

Because of the importance of Rule 144, I have summarized its provisions in Attachment 2. I encourage you, however, to consult with me before effecting any transaction in the Company's equity securities.

The objective of this letter and its attachments is to give you a general and non-technical overview of significant portions of the law that presently appear to be applicable to directors and executive officers of the Company. We have not attempted to cover every nuance or refinement, or to deal with every circumstance that is theoretically foreseeable; therefore, you may have questions as to this material in general or with respect to a particular situation. Should this be the case, please feel free to call John Landes or Catherine Vaczy at (212) 645-1405.

IMCLONE SYSTEMS INCORPORATED

20

Principal: CN=Thomas Gallagher/O=ImClone
ForwardedFrom: CN=Thomas Gallagher/O=ImClone
$Mailer: Lotus Notes Release 5.0.8 June 18, 2001
$MessageID: <OFD3C253ED.2BDA441C-ON85256B26.00818C16@LocalDomain>
INetFrom: ThomasG@imclone.com
Recipients: <thomasg@imclone.com>
MailOptions: 0
SaveOptions: 1
Form: Memo
From: CN=Thomas Gallagher/O=ImClone
AltFrom: CN=Thomas Gallagher/O=ImClone
Logo: StdNotesLtr23
useApplet: True
Sign: 0
DefaultMailSaveOptions: 1
SendTo: thomasg@imclone.com
Subject: Insider Trading Policy
EnterSendTo: thomasg@imclone.com
$UpdatedBy: CN=Thomas Gallagher/O=ImClone
ID: OFD3C253ED:2BDA441C-ON85256B26:00818C16
To: thomasg@imclone.com
Importance: Normal
Delivery priority: Normal
Delivery report: Report only if message is not delivered
Mood stamp: Normal
Creation time: 12/18/2001 06:35:00 PM
Last modified time: 12/18/2001 06:53:19 PM
Last access time: 12/18/2001 06:53:19 PM

On Friday December 14, 2001 I exercised and sold 20,000 shares of non-qualified stock, which was granted as part of an employee stock option plan. The average share price was 69.95. The sale of stock was animated by discussions with my brother the previous week in which he counseled that it would be irresponsible for me not to sell stock since there was plenty remaining to vest, and that more would be issued. He thought I should sell all that I have access to at this time.

Prior to December 14, 2001, I became aware that ImClone Systems may be added to the NASDAQ 100, causing a jump in the stock. Such a jump seemingly occurred midweek. Wanting to reduce my risk of leaving most shares unexercised and sensing that by the time the NASDAQ 100 decision was made Monday any jump in stock price would have dissipated, I sold the 20,000 shares.

Never having to seek approval for exercising stock before I did not think to inform Cathy Vaczy of my decision to sell. I have exercised and sold stock on several occasions throughout my years at ImClone Systems, first as a Research Scientist and as a Senior Director of the Company, never having sought pre-approval to conduct such transactions. Now, as an Assistant Vice President, I did not realize that I should do so.

On Tuesday, December 18, 2001, Cathy Vaczy reminded me in a conversation that I am subject to the Insider Trading Policy of the Company. She further informed me that select members of Senior Management have been aware that the FDA may not accept our BLA

filing. This information became known to them sometime last week and that this week they were moving to deal with the issue with members of Bristol-Myers. Today was the first time this information was made known to me. As patent counsel to the Company, I am not routinely advised of issues having to do with our BLA filing and matters before the FDA.

The sale of ImClone stock on December 14 was done without any knowledge of the status of the Company's BLA filing. Indeed the sale was unrelated to any information not known to the public.

---- Forwarded by Thomas Gallagher/ImClone on 12/18/2001 06:35 PM ----

Cathy Vaczy
12/18/2001 04:44 PM

To: Peter Bohler
Richard Crowley/ImClone@ImClone, Charles Dunne/ImClone@Im
Goldstein/ImClone@ImClone, Daniel S. Lynch/ImClone@ImClone,
Needle/ImClone@ImClone, Gary Pauller/ImClone@ImClone, Andr
Tarnowski/ImClone@ImClone, Larry Wite/ImClone@ImClone, Har
Waksal/ImClone@ImClone, Lily Lee/ImClone@ImClone, Michael H
cc: Kurt Elster, T
Landes/ImClone@ImClone
Subject: Insider Tradi

As you know, ImClone Systems maintains an Insider Trading Policy which applies to all open market transactions of shares of ImClone Systems common stock by directors, officers and other employees of the Company. You are reminded that Section IV(A) of the policy requires that all officers of the Company (i.e., those with the title of AVP and above) receive authorization from the Office of the General Counsel (specifically, John Landes or myself) in advance of any open market transaction in ImClone Systems common stock. This enables us to assess whether there exists material non-public information at that time that is of such a sensitive nature that it is inappropriate for management to be trading in the open market. Open market transactions include purchases of stock and sales of stock, whether on option exercise or otherwise. Effective immediately, this policy is being expanded as follows:

-request for authorization to engage in a transaction in ImClone Systems common stock by an officer must be in writing and directed to John Landes or myself. This request may come in the form of an e-mail and should briefly describe the transaction (e.g., exercise of 1,000 options and sale of the shares, purchase of 1,000 shares, sale of 1,000 shares held in brokerage account)
-authorization from John Landes or myself must be received in writing; such authorization will specify the date and time it is given
-written authorizations may only be relied upon by the officer for 24 hours from the date and time that it is given.

Please feel free to call me with any questions you may have regarding the foregoing.

Catherine M. Vaczy
Vice President, Legal & Associate General Counsel
ImClone Systems Incorporated
Phone: (646) 638-5032
Fax: (212) 645-2770

21

From: Cathy Vaczy/ImClone

To: All

Subject: Company-wide black-out

Date: 12/21/2001 03:26:18 PM EST

As many of you know, the FDA is required to tell us by the end of next week whether the filing of our BLA for Erbitux has been accepted and whether the file will be granted expedited review. Given the importance of this news, we believe employees should not trade ImClone stock until we receive definitive information from the FDA and a press release is issued. Accordingly, we have put into effect a company-wide black-out in trading in ImClone stock as described in Section IV(D) of ImClone's Insider Trading Policy.

Please contact the Legal Department should you have any questions.

22

Principal: CN=Michael N. Needle/O=ImClone
ForwardedFrom: CN=Michael N. Needle/O=ImClone
$AutoSpell: 1
Form: Memo
AltFrom: CN=Michael N. Needle/O=ImClone
Logo: StdNotesLtr7
useApplet: True
Sign: 0
DefaultMailSaveOptions: 1
Subject: Proposed final draft of 0023 paper
SendTo: martin.birkhofer@bms.com; fabio.benedetti@bms.com; matthew.ros@bms.com; CN=Lily Lee/O=ImClone@ImClone; harlan@imclone.com; CN=Thomas Gallagher/O=ImClone@ImClone; CN=Michael.Bailey/O=ImClone@ImClone
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$StorageTo: 1
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$MessageID: <OF7F882D67.35E89F12-ON85256B29.0072080A@LocalDomain>
From: CN=Michael N. Needle/O=ImClone
INetFrom: Mneedle@imclone.com
$UpdatedBy: CN=Michael N. Needle/O=ImClone; CN=notes1/O=ImClone
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$MsgTrackFlags: 2
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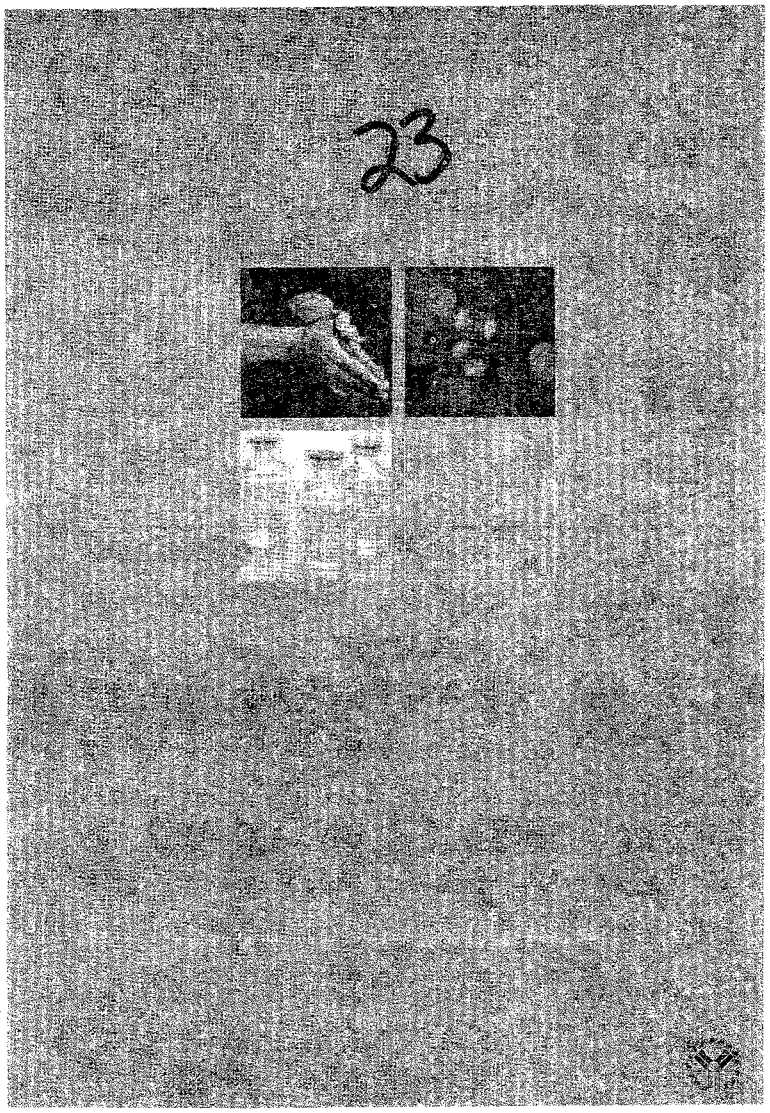
To: martin.birkhofer@bms.com
Importance: Normal
Delivery priority: Normal
Delivery report: Report only if message is not delivered
Mood stamp: Normal
Creation time: 12/21/2001 03:45:31 PM
Last modified time: 12/21/2001 03:52:25 PM
Last access time: 12/21/2001 03:52:25 PM
Number of attachments: 1

Attached is a final draft of the 9923 paper from Len Saltz and colleagues. Len has incorporated comments both from BMS/ImClone and the co-authors (mostly Hochster). He is holding the paper until after we hear from FDA. Please circulate as you see fit. Len will be anxious to submit as early as possible in 2002.


23

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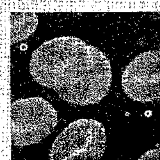


is committed to advancing oncology care by developing a portfolio of targeted biologic treatments, designed to address the medical needs of patients with a variety of cancers. The Company has focused its efforts on three clinical programs, which include growth factor blockers, cancer vaccines and angiogenesis inhibitors. ImClone Systems' strategy is to become a fully integrated biopharmaceutical company, taking its development programs from the research stage to the market. ImClone Systems is headquartered in New York City with additional administration and manufacturing facilities in Somerville, New Jersey.

Pictured: Angel Santiago (Mar 5, 1965–May 9, 2001). [illegible] 2001, ImClone Systems lost one of its most precious assets, a bright and dedicated employee. Angel Santiago joined ImClone Systems in 1997 as a Research Scientist in Molecular and Cellular Biology. Angel fought a courageous battle before finally succumbing to leukemia. He was passionate about his work, a friend to many and a devoted husband and father. As a talented scientist Angel played a major role in the early successes at ImClone Systems. His contributions and companionship are sorely missed.

To Our Shareholders:

For ImClone Systems Incorporated, 2001 was a year filled with achievement in many areas of the Company's business. It was also a year that ended with the very disappointing news of the decision by the U.S. Food and Drug Administration (FDA) not to accept the ERBITUX™ Biologics License Application (BLA) as submitted. This decision came in the form of a "Refusal To File" (RTF) letter from the FDA with respect to ERBITUX, our Epidermal Growth Factor Receptor (EGFR) monoclonal antibody. In spite of this disappointment, as we look back and ask, "Have we made significant progress in furthering the strategic objectives of the Company, and are we substantially closer to having a commercially available oncology product than we were one year ago?", we can only conclude that 2001 was a very successful year indeed. While the events at the end of 2001 have posed difficult challenges for the Company, the advances made during the year should not be overlooked, and through everything, we continue to focus our efforts on moving ERBITUX through the clinic and toward commercial viability.

The progress made in 2001 spanned many critical areas of the Company's business, including clinical development, research and discovery, manufacturing, intellectual property, strategic partnering and strengthening of our management team. All of these advances have enhanced our ability to move forward with the development of our first product candidate, ERBITUX. Importantly, we should be able to leverage this progress as we develop other product candidates and research programs beyond ERBITUX.

We began 2001 by receiving Fast Track Designation from the FDA for ERBITUX for the treatment of irinotecan-refractory colorectal carcinoma. Such designation may be granted to a drug if it is intended for the treatment of a serious or life-threatening condition, and it demonstrates the potential to address unmet medical needs for such a condition. With Fast Track Designation, the FDA facilitates drug development and expedites drug review. It is important to note that even with the regulatory setbacks experienced with the BLA, we still retain Fast Track Designation, although it will take time to resubmit our application for approval to the FDA.

Our intellectual property portfolio for ERBITUX was strengthened in February with the issuance of U.S. Patent No. 6,217,865, which covers the therapeutic combination of any EGFR monoclonal antibody and anti-neoplastic agents, such as chemotherapeutic agents, for use in the treatment of cancer. The issuance of this patent has solidified our competitive position regarding the therapeutic use of ERBITUX in combination with any anti-neoplastic agent.

Our management team was strengthened last year by filling key executive positions. Daniel S. Lynch and Michael J. Howerton, both former Bristol-Myers Squibb executives, and Dr. Lily Weiyee Lee joined the Company as Senior Vice President of Finance and Chief Financial Officer, Vice President of Business Development and Vice President of Regulatory and Biostatistics, respectively. These additions will help the Company continue to strengthen its senior management team and navigate the complexities of the biopharmaceutical world.

In the area of research and discovery, the Company presented findings on Vascular Endothelial Growth Factor Receptor-1 (VEGFR-1). This is a relatively new area of study that we believe plays a key role in

However difficult the year-end events were, we believe that 2001 will be viewed as a fruitful and productive year for ImClone Systems.

tumor angiogenesis (new blood vessel formation). At the annual meeting of the American Association for Cancer Research (AACR) in March 2001, ImClone Systems' scientists presented findings which demonstrated that the use of a monoclonal antibody that targets VEGFR-1 resulted in significant inhibition of tumor angiogenesis and tumor growth in human tumor models of breast cancer. Among the other presentations made by the Company during the AACR meeting were positive preclinical findings on our novel recombinant IMC-TRPx3 protein-based melanoma vaccine. The findings demonstrated that the IMC-TRPx3 vaccine elicited antibody and cellular immune responses in vaccinated mice. Additional findings showed that immunization with the vaccine could protect from the introduction of melanoma cells. These programs are continuing to be aggressively pursued.

The Company has a variety of other research programs currently underway in addition to IMC-TRPx3 and VEGFR-1.

The Company has recently completed the preclinical phase of testing on our IMC-GP75 vaccine candidate. IMC-GP75 is a DNA vaccine containing the genetic code for gp75, a tumor antigen that is prevalent in melanoma. Preclinical studies using IMC-GP75 have shown its ability to significantly reduce the number of melanoma lung metastases in animal models. We plan to advance IMC-GP75 into clinical trials in 2002. This program represents yet another example of the Company's fast-growing capabilities that enable us to transform basic research into product candidates that are being tested in the clinic.

Another encouraging research program focuses on the development of therapeutics against VE-cadherin, an "adhesion molecule" expressed on endothelial cells. VE-cadherin is used by endothelial cells to adhere to one another in order to organize into vascular tubes, a necessary step in the formation of new blood vessels. Preclinical studies of VE-cadherin monoclonal antibodies have shown their ability to inhibit angiogenesis, tumor growth and metastasis by blocking the ability of VE-cadherin to form tubular structures. Our scientists are currently optimizing antibodies against VE-cadherin to specifically target this molecule.

ImClone Systems also invested in the expansion of its chemistry and gene discovery and bioinformatics capabilities in 2001. The Company has dedicated significant resources to hiring a talented group of scientists and establishing new laboratory facilities for its chemistry department. This department has been charged with identifying and developing novel therapeutics that interrupt the internal cancer cell-signaling pathways that enable tumors to grow, spread and survive cell damage. The enhancement of our capabilities in all of these areas is part of the Company's effort to ensure that it continues to develop and advance novel drug candidates through its pipeline and into the clinic.

We are proud of the pipeline of potential products generated by our research team at ImClone Systems.

During the year, we greatly expanded our clinical experience with ERBITUX™. In May 2001, during the meeting of the American Society of Clinical Oncology (ASCO), we presented findings from a number of Phase II clinical studies of ERBITUX in several cancer types, including refractory colorectal and head and neck cancers, and for the first time, in pancreatic cancer. Findings from a Phase II clinical study of ERBITUX and the anti-cancer agent gemcitabine in patients with pancreatic cancer demonstrated encouraging preliminary results. Specifically, it was shown that the combination therapy could shrink tumors by greater than 50 percent in some patients, as well as demonstrating a trend in the combination's impact on overall patient survival.

In addition, the Company initiated a new program to evaluate several combinations of ERBITUX® and currently FDA-approved agents for the treatment of non-small cell lung cancer. Three clinical trials of ERBITUX were opened in the non-small cell lung cancer indication last year. We plan to continue to expand the ERBITUX clinical program by initiating clinical trials in additional EGFR-positive tumor types, in order to address the broadest population of patients who may benefit from the treatment.

ImClone Systems also conducted a Phase II study to evaluate ERBITUX as a single agent therapy in patients with irinotecan-refractory colorectal cancer. The findings from that study, as well as data from other ERBITUX trials, have been submitted for presentation at the 2002 American Society of Clinical Oncology annual meeting.

The Company has also made progress in the BEC2 cancer vaccine program and in the development of our Vascular Endothelial Growth Factor Receptor-2 (VEGFR-2) monoclonal antibody program. During 2001, the Company received milestone payments from Merck KGaA, our European partner for BEC2, for reaching the halfway mark in both enrollment and randomization of patients in our Phase III clinical trial of BEC2 in Limited disease small cell lung cancer. In the VEGFR-2 program, the Company continues to plan for the initiation of additional clinical trials to evaluate safety and pharmacokinetics in anticipation of the drug supply requirements that would commence upon approval of ERBITUX by the FDA. The Company has significantly advanced its manufacturing capability with the completion of a 39,000-liter biologics manufacturing facility on our growing Somerville, New Jersey campus. The construction of the facility provided new insights on construction and engineering practices used to build out a plant designed for the production of biologic drugs. The Company has completed the manufacture of test batches of ERBITUX, which will be used to support FDA licensure of the facility for the production of commercial drug supply. Once licensed, the facility will produce a significant portion of the commercial supply of ERBITUX.

We continue to focus our efforts on developing ImClone Systems into a fully integrated, biopharmaceutical company. Our manufacturing capabilities remain a cornerstone in building a strong commercialization infrastructure to support this effort. To that end, we are currently in the planning and engineering stage for the construction of a multi-product, biologics manufacturing facility with a capacity of under 100,000 liters. When completed, the new facility will have the capacity to supplement the commercial supply of ERBITUX, as well as the manufacture of other biologic drugs being developed by our researchers.

In September, ImClone Systems entered into a landmark strategic partnership with Bristol-Myers Squibb (BMS) for the co-development and co-commercialization of ERBITUX in the United States, Canada and Japan. The transaction with BMS consisted of two parts: a commercial agreement for ERBITUX, as well as an agreement from BMS to buy approximately 20 percent of ImClone Systems stock from existing shareholders through a tender offer. The commercial agreement, as amended, provides ImClone Systems with financial security through an initial infusion of $200 million, and then an additional $140 million. The Company will also receive 39 percent of the revenues derived from sales of ERBITUX in the United States and Canada. The Agreement calls for the Company to receive an additional $360 million upon the achievement of certain milestones. The transaction was designed to enable ImClone Systems to leverage BMS' premiere oncology sales force and extensive network of oncology contacts and resources in order to rapidly achieve the broadest possible distribution of ERBITUX. Additionally, the stock purchase was structured in a way that would enable all of our shareholders to benefit from the growth and value of the Company by selling part of their holdings for BMS at $70 a share, which was approximately a 20 percent premium to the share price at the time the agreement was signed.

Shortly after the BMS agreement, ImClone Systems announced that it had completed its rolling BLA submission to the FDA for ERBITUX in the treatment of irinotecan refractory colorectal cancer. The BLA, which consisted of many sections of information and data in areas including safety, manufacturing and clinical experience, represented the culmination of over ten years of research and clinical study.

Our efforts to build ImClone Systems into a financially successful biotechnology enterprise were recognized when the Company was added to the Nasdaq-100 Index®, which represents 100 of the largest non-financial companies listed on the National Market tier of the Nasdaq.

In December 2001, ImClone Systems confronted its biggest challenge when the FDA issued its RTF letter. The deficiencies outlined in the RTF letter prevented the FDA from being able to conduct a thorough and scientific review of the clinical portion of the submission. Despite our disappointment, we

continue to believe that ERBITUX™ will be a viable product for the Company, and we are resolved to address the FDA's concerns in order to put us back on the path to product commercialization. Since December, ImClone Systems has set out to meet and overcome the numerous additional challenges that have followed receipt of the RTF letter. These challenges include investigations by government authorities and class action litigation. It is our belief that one of the important ways to assess a Company is to determine how well it faces adversity and rises to the challenges put before it. We want to assure you that management will work hard to meet these challenges and prevail.

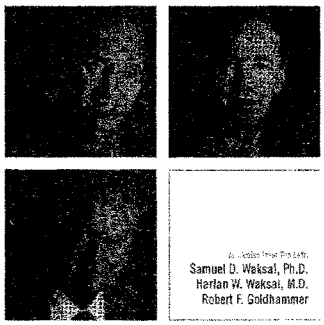
In February 2002, ImClone Systems had a productive meeting with the FDA to discuss how to address its concerns with the ERBITUX BLA. During the course of that meeting, we discussed an approach with the FDA for refiling the BLA incorporating data from a Merck KGaA Phase II clinical study of ERBITUX in refractory colon cancer in conjunction with re-analyzed clinical data from ImClone Systems' U.S. Phase II clinical trials.

We have also successfully resolved the issues of contention that arose between ImClone Systems and BMS as a result of the RTF letter and the events that followed. Recognizing that a strong partnership was in the best interest of the future of ERBITUX and the patients we hope to help, ImClone Systems and Bristol-Myers Squibb agreed to certain changes in the economics of the commercial agreement.

However difficult the year-end events were, we believe that 2001 will be viewed as a fruitful and productive year for ImClone Systems. Our efforts have resulted in encouraging developments in both early-stage research and in our clinical programs, most notably ERBITUX. In addition to scientific progress, the Company implemented several strategic initiatives that resulted in many accomplishments, including our landmark agreement with BMS, and the dramatic expansion of our manufacturing capabilities. The collective successes achieved by the Company in 2001 have brought us closer to our ultimate goal of becoming a biopharmaceutical company with the capabilities necessary to develop and commercialize its own oncology products for the treatment of patients with cancer.

Our focus in 2002 will be to move forward with the clinical development of ERBITUX. We have an approach in place for resolving the FDA's concerns over the BLA. We also have strong partnerships in place with both BMS and Merck KGaA. ImClone Systems is optimistic about the year ahead. We will continue to expand our clinical experience with ERBITUX and our other product candidates, and we will use the lessons learned in 2001 to build ImClone Systems into a stronger, more experienced, fully integrated biopharmaceutical company.

Every year we reserve the close of this letter to thank our employees as well as thanking you, the investor. In no other year have those thanks meant as much to us as they do this year. Our employees have demonstrated a remarkable combination of focus, dedication and resiliency in meeting the year's challenges, and for that we are extremely grateful. As investors, we want to thank you for your continued dedication and loyalty to ImClone Systems and its mission to develop drugs to fight serious disease. We want to assure you that management will endeavor to justify your confidence.



(L-R) Samuel D. Waksal, Ph.D.
Harlan W. Waksal, M.D.
Robert F. Goldhammer

Samuel D. Waksal, Ph.D.
President and CEO

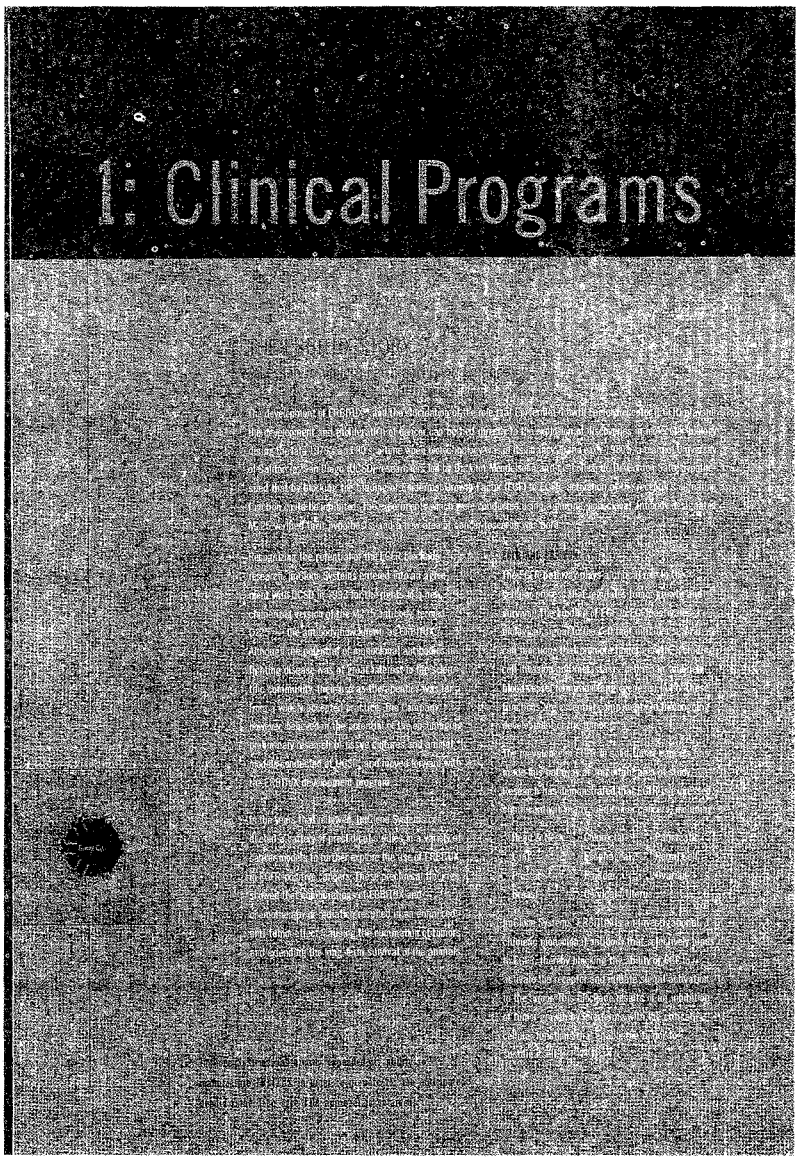
Harlan W. Waksal, M.D.
Executive Vice President and COO

Robert F. Goldhammer
Chairman of the Board

ImClone Systems is dedicated to developing novel therapeutic products in the field of oncology. Our efforts have resulted in a broad spectrum of innovative targeted cancer treatments with applications in multiple tumor types. As members of the oncology community, we are **committed** to providing quality products to cancer patients. In efforts to fulfill this statement, ImClone Systems fosters the integration of the principles of teamwork and scientific integrity into all facets of the Company's activities. We believe that these values will benefit patients, physicians, and our employees while creating value for our shareholders.

I originally planned on being an artist. I wanted to make movies. But science always interested me. When I was in sixth grade I won an award for my carbon atom. I made it out of Christmas lights. To me, there is such a sense of satisfaction and accomplishment at the moment you discover something for the first time. There is also a very artistic side to science. To solve complex problems, you have to think creatively. • I believe that my role as a research scientist is to use my technical know-how and my creativity to further what is known about why cancer works the way it does.

Jim Huber
Research Scientist
Immunology, *6 years*


1: Clinical Programs

ERBITUX® has been in clinical study since 1995, and has been evaluated in all three phases of clinical testing. Since the Company initiated the clinical program, approximately 3,000 patients have received ERBITUX, mostly as part of a combination regimen with either chemotherapy or radiation, in a variety of disease stages and cancers, including colon cancer, head and neck cancer, pancreatic cancer and non-small cell lung cancer.

The research conducted to date has shown that when used alone or in combination, ERBITUX has demonstrated an acceptable safety profile. The primary side effect observed in clinical studies to date has been an acne-like rash that is usually resolved following cessation of treatment. In rare cases, anaphylaxis has been observed during the initial dose of ERBITUX. This side effect has been associated with all antibody-based therapies. In addition, ERBITUX has not been observed to cause the types of side effects typically seen in treatment with chemotherapy and radiation.

At present, 11 Phase II and III clinical trials are being conducted in patients with colorectal, head and neck, pancreatic or non-small cell lung cancer, which was added to the program last year in 2002. The Company plans to expand its clinical experience in pancreatic and colon cancers with the initiation of large Phase III clinical trials. The Company also is planning to initiate studies in additional indications such as ovarian cancer, cervical cancer and esophageal cancer.

ImClone Systems has greatly expanded its ability to manufacture ERBITUX in order to prepare for the anticipated need for the drug once FDA approval is obtained. In late 2001, the Company completed its first commercial manufacturing facility dedicated to the production of ERBITUX. Later that year, the Company broke ground on a new multi-product biologics manufacturing facility with a capacity of up to 1,000 liters.

Since receipt of the "CR" letter issued by the FDA, ImClone Systems has met with the FDA and sought its guidance on the steps necessary to proceed with a resubmission of the ERBITUX BLA for the treatment of irinotecan-refractory colorectal cancer. During 2003, the Company in cooperation with its partners Merck KGaA and Bristol-Myers Squibb will focus its efforts and resources on compiling the information and data needed for the resubmission of a revised BLA and getting ERBITUX approved as quickly as possible.

ImClone Systems was already engaged in the area of cancer vaccine research. The Company's most advanced product candidate in the vaccine area is BEC2, an investigational monoclonal antibody that is designed to prevent or delay the recurrence of certain types of tumors when used with Bacillus Calmette-Guerin (BCG) as an immune stimulant.

The BEC2 vaccine mimics GD3, a tumor antigen found on the cell surface of certain types of cancers. By mimicking this antigen, BEC2 appears to stimulate a stronger immune response to cells expressing natural GD3. In limited pilot studies of BEC2 in patients with limited disease small cell lung carcinoma, preliminary findings suggest that BEC2 has the potential to stimulate the body's immune system to identify and eliminate residual tumor cells, prevent recurrence of tumors, and prolong survival in this tumor type.

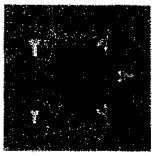
ImClone Systems and its partner Merck KGaA are jointly conducting a Phase III clinical trial of BEC2 in patients with limited disease small-cell lung cancer. In 2001, the study reached the halfway mark in the patient enrollment and randomization. Phase II studies have also been conducted using BEC2 in patients with melanoma.

The advances made in molecular biology and cancer research have taught us that tumors rely on the formation of new blood vessels, referred to as angiogenesis, for their ability to take in nutrients and oxygen in order to grow and survive. Angiogenesis occurs through the interaction of proteins. One such protein, Vascular Endothelial Growth Factor (VEGF), has a receptor found almost exclusively on growing endothelial cells, known as Vascular Endothelial Growth Factor Receptor-2 (VEGFR-2). The binding of VEGF to VEGFR-2 activates a biological signal that in turn instructs the cells to form new blood vessels.

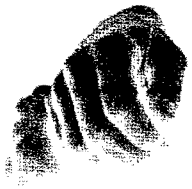
Over the past year, ImClone Systems has been developing a fully human monoclonal antibody, designated IMC-2C6, that is designed to target and block VEGFR-2. IMC-2C6 is highly selective to binding with VEGFR-2 and in blocking the ability of VEGF and other proteins from activating the receptor and its biologic signal.

The Company is currently in the process of planning clinical studies to be initiated in 2003 to evaluate the safety and pharmacokinetics of IMC-2C6 in patients with solid tumor cancers and acute myelogenous leukemia.

Marie Prewett
Scientist
Immunology, *9 years*



I have always derived satisfaction from the idea of taking broken things and fixing them. Years ago, I participated in a project at the University of Pennsylvania to restore a 1920's pipe organ. As the project moved forward, you could see the progress being made in small increments, until finally you could see the beginnings of the finished product. My work as a researcher is similar because I get to watch our compounds move forward from the laboratory to the clinic. • I've been involved in the ERBITUX® program for seven years. I was involved in the design and execution of preclinical studies and now it's at the clinical and regulatory review stage. Knowing that I have had a role in its development makes me feel very satisfied, much as I did with that old pipe organ at Penn.



2: Preclinical Pipeline

THE DISCOVERY RESEARCH AND PRECLINICAL PIPELINE

Pursuing Cutting-Edge Science to Combat Cancer

The scientists in ImClone Systems' Research Department are exploring solutions to the complexities of combating cancer at the cellular and molecular level. Each day they push the boundaries of what is known and understood about the biological mechanisms that cause cancer and then translate these discoveries into a pipeline of emerging drugs. In addition, external partnerships and collaborations with high caliber academic investigators continue to play a key role in ImClone Systems' quest for novel cancer therapeutics. The Company's oncology research programs generally fall into three categories: angiogenesis inhibition, cancer vaccines, and growth factor receptor antagonists.

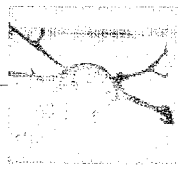
1. ANGIOGENESIS INHIBITION

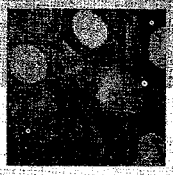
Cancerous tissue thrives on the same nutrients that feed the body's healthy tissue. These nutrients are delivered by intricate networks that allow the tumor to survive, grow and disseminate to other tissues. When a tumor needs to grow and spread, it relies on the formation of new blood vessels, a process referred to as angiogenesis. Scientists have discovered that interfering with the tumor's ability to grow new blood vessels and maintain its supply of nutrients and oxygen essentially starves the tumor to death.

Researchers at ImClone Systems are exploring several novel pathways that are essential to the process of angiogenesis. The Company is developing a wide array of therapeutics for preventing angiogenesis through the inhibition of a diverse group of cell surface receptors and molecules.

Vascular Endothelial Growth Factor Receptor-2 (VEGFR-2)

VEGFR-2 (also known as KDR) remains a major area of preclinical research at ImClone Systems. In support of the VEGFR-2 clinical program, the Company continues to examine the utility of VEGFR-2 antibodies as angiogenesis inhibitors against various tumor types, and in combination with various chemotherapeutic drugs or radiation. ImClone Systems' scientists and their academic collaborators have published a number of key findings over the past year that further define VEGFR-2 as an important target in cancer therapy. One such finding demonstrated the utility of combining VEGFR-2 antibody and a new, experimental approach to cancer treatment referred to as "metronomic" therapy, which involves the use of low, non-toxic doses of cytotoxic drugs. The Company and its academic partners have also characterized the role of VEGFR-2 in other fields of research including hematopoiesis, immunobiology and neurobiology, suggesting potentially new areas for VEGFR-2-targeted therapies in related diseases.





Bill Spinks

Liz Cosen

VEGFR-1 (also known as flt-1) is found on the surface of several cell types, including endothelial cells, blood cells and certain tumor cells, such as breast cancer cells.

ImClone Systems has accumulated preclinical data on the use of VEGFR-1 specific antibodies to inhibit breast cancer. Research presented by Company scientists last year demonstrated for the first time ever, that use of a VEGFR-1 monoclonal antibody arrested breast cancer growth through two different mechanisms of action. The research showed that the VEGFR-1 antibody inhibited tumor angiogenesis by blocking VEGFR-1 on blood vessels as well as directly affecting the growth of VEGFR-1 positive breast tumor cells.

Efforts are currently ongoing to develop a therapeutic VEGFR-1 monoclonal antibody for evaluation in pre-clinical studies to assess its safety and activity.

VE-cadherin is a molecule expressed exclusively on the endothelial cells that line blood vessels. The role of VE-cadherin in the angiogenic process is paramount because it is critical for the proper organization of endothelial cells into vascular tubes, a necessary step for the formation of new blood vessels.

The Company has conducted preclinical studies using monoclonal antibodies developed against VE-cadherin. These antibodies are able to inhibit angiogenesis, tumor growth and metastasis by blocking VE-cadherin's ability to act as an adhesive for endothelial cells, thereby blocking their formation into tubular structures. ImClone Systems scientists are in the process of developing a therapeutic VE-cadherin antibody for evaluation in preclinical studies to assess safety and efficacy.

ImClone Systems' cancer vaccine research program is identifying new targets and immunization approaches to engage the immune system in attacking cancerous cells. The Company's efforts in this area currently are focused on the development of vaccines to stave off the recurrence of melanoma, a deadly form of skin cancer.

The IMC-gp75 vaccine is a recombinant DNA vaccine that contains the genetic code for gp75, a frequently expressed melanoma antigen. Preclinical studies of IMC-gp75 have demonstrated that mice immunized with the vaccine produced a strong immune response to gp75 and melanoma cells that express this antigen. Preclinical studies have also shown that immunization with IMC-gp75 can protect mice from growth of melanoma tumors and metastases. ImClone Systems plans to initiate Phase I studies of IMC-gp75 in patients with melanoma in 2002.

Commitment

IMC-TRPx3 Recombinant Protein Vaccine

ImClone Systems is developing a vaccine comprised of a number of human melanoma proteins. In preclinical testing, the IMC-TRPx3 vaccine has demonstrated the ability to produce antibody and cellular immune responses against melanoma cells in mice. Additionally, preclinical findings have shown that mice vaccinated with IMC-TRPx3 and challenged with melanoma tumor cells have a significantly reduced number of lung metastases as compared with a control group.

3. GROWTH FACTOR RECEPTOR ANTAGONISTS

ImClone Systems' scientists are studying a number of growth factor receptor targets expressed by tumor cells. These growth factor receptors are intimately involved in key processes of tumor cell growth and survival. The development of new drugs that block the function of these receptors is an active area of research at ImClone Systems. One such Growth Factor Receptor that the Company is investigating is flt-3.

flt-3 Research

The flt-3 receptor is frequently expressed in human leukemias and is believed to be important for tumor growth and progression. The Company is currently developing monoclonal antibodies against the flt-3 receptor to evaluate their activity in preclinical studies.

4. GENE DISCOVERY

A first step toward developing new biologic therapies is discovering the role that different genes play in the development of disease. In collaboration with academic partners at Princeton University and the University of Pennsylvania, and with scientists at Celera Genomics, ImClone Systems is building a library of unique and proprietary gene sequences that has the potential to yield new targets in the fight against cancer and other diseases.

The Company plans to continue expanding its capabilities in this area during 2002.

5. SMALL MOLECULE DRUG DISCOVERY

Over the past year, ImClone Systems has expanded its effort to build an internal small molecule drug discovery program. The Company has assembled an interdisciplinary team of scientists including medicinal chemists, molecular and cell biologists, automation and screening specialists and computational scientists. The drug discovery program will utilize chemical and biological research to identify novel cancer targets located both inside and outside the cell that are suitable for rational drug design. The long term goal of this effort is to add novel small molecule drug candidates to the Company's existing antibody pipeline.

Currently, the main research focus of the small molecule program is the discovery of novel inhibitors of kinases, the key enzymes of the cancer cell life-cycle machinery. Members of this "kinase panel" include EGFR and VEGFR-2, targets for which the Company has already established a considerable body of research. The Company is working toward achieving a better potency and toxicity profile for small molecule candidates. This effort has culminated in the identification of potent small molecule inhibitors against proprietary targets.

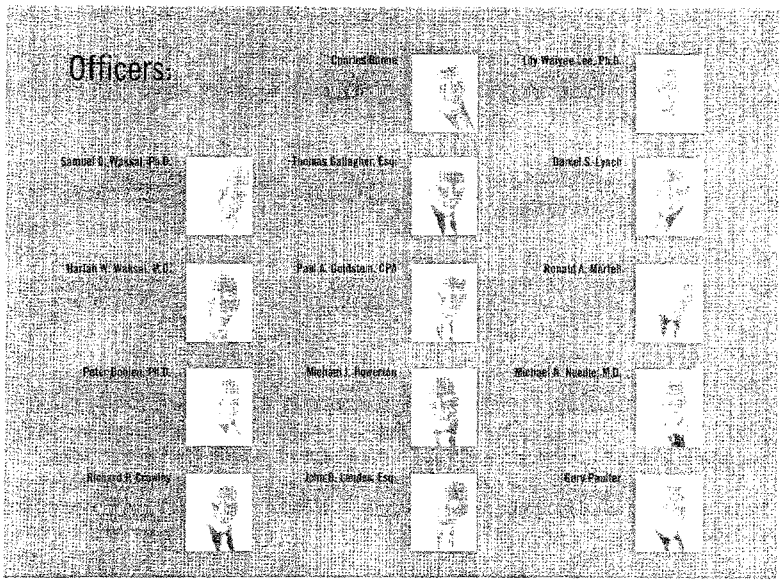
The Company plans to further expand its small molecule drug discovery effort through 2002 and 2003 building chemistry into a core competency of the research department.

Every day, ImClone Systems' scientists push the boundaries of what is known and understood about the biological mechanisms that cause cancer.

Maria Prieto: I really was. I thought that I wanted to be a doctor like my father, because I wanted to help people. I do not regret doing that, and I'm still interested in basic sciences, especially in terms of how all the new basic technologies for treating disease. So I call it work-arounds. Professionally, I've grown up at Millipore Sigma. I think about our mission all the time. My brother died of cancer, and so did my cousin. The fight against cancer is always, now, my goals. When the company was smaller, we would have employee meetings in our small boardroom to get updates on the clinical trials. When we'd hear about a patient that was responding well to the treatment, it would make me feel really great. We're lucky to have made some—many—headways now, but I still love to hear about the clinical trials.

Maria Prieto

Haijun Sun



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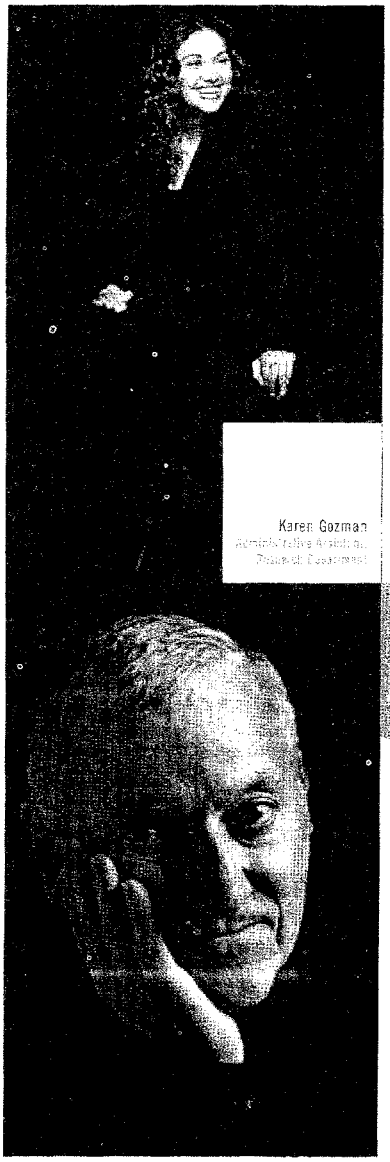


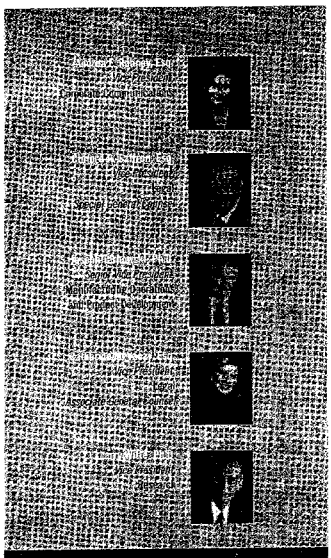
Karen Gozman

Dr. Nick Giorgio

Dr. Nick Giorgio, 16 years: I've been working in protein chemistry for 45 years. During that time I've seen tremendous achievements made in understanding the complexities of proteins and the role that they play in diseases, like cancer. Now I am seeing these achievements translated into clinical candidates. • In the years to come I would like to see our research translate into therapies for cancer. That's really the thrust of ImClone Systems. We started as a diagnostic company in 1986, and I was employee number 10. Back then, the Company was just a couple of labs and very little else, including equipment! Today, we are a Company with a number of compounds in clinical trials, and many in the research stage. We have a great group of researchers and the caliber of science we are conducting is high.

Jimmy Carter
Staff Member
Facilities, *17 years*

Name a support job at ImClone Systems and I think I've done it. Every day is different. That's the way I like it. Doing one thing all the time has never been enough for me. The first thing I learned when I came to work at the Company seventeen years ago was scientists are a pretty unique bunch of people. You can figure on that, but they are also kind and compassionate. They have become my friends over the years. I've lost a lot of my family to cancer. At work, I like to think about what the scientists are doing to put a few more years on people's lives, and I give them applause for it. I think they're doing a wonderful job.



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Certified Public Accountants
KPMG LLP (Princeton, NJ)

Common Stock
ImClone Systems Incorporated is traded on the NASDAQ National Market under the symbol: IMCL

The following table sets forth prices for the indicated periods for the fiscal year ended December 31, 2001.

	High	Low
1st Quarter	$44.25	$23.38
2nd Quarter	$56.30	$26.50
3rd Quarter	$59.69	$40.80
4th Quarter	$75.45	$43.35

Investor Information

Company Reports
For additional information concerning the Company, including copies of any exhibits listed in this annual report (upon payment to the company of its reasonable expenses in so furnishing such exhibits), please contact:

Andrea F. Rabney, Esq.
V.P., Corporate Communications
ImClone Systems Incorporated
180 Varick Street
New York, NY 10014
Tel: 212.645.1405
Fax: 212.645.2054

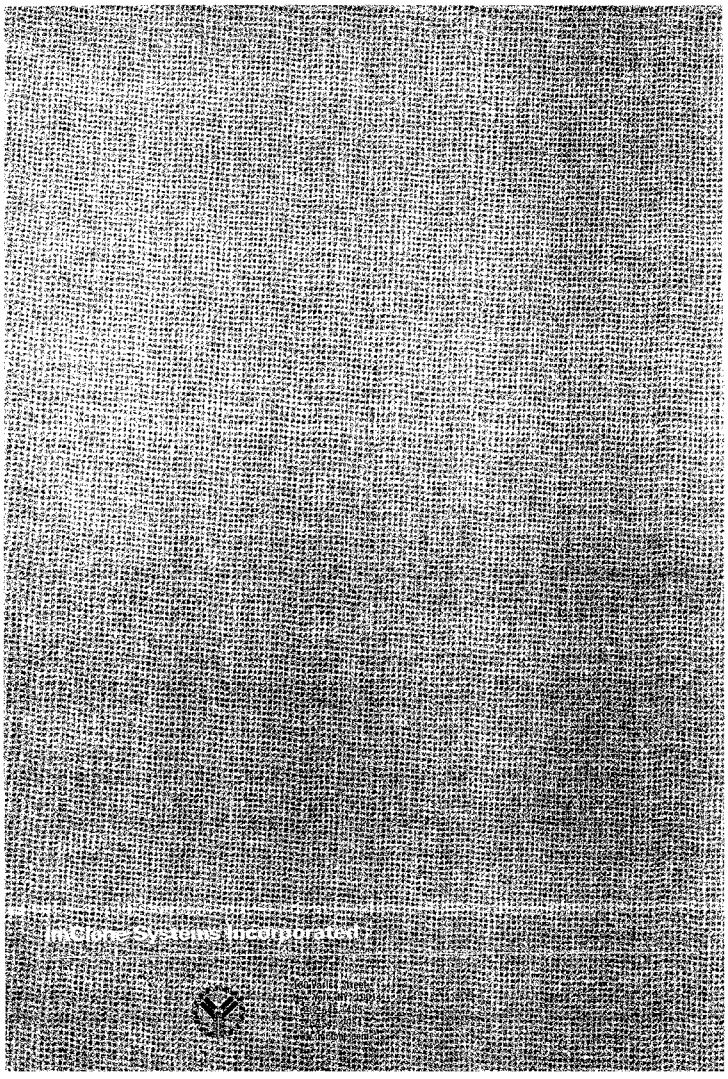
Annual Meeting
The Annual Meeting of Stockholders will be held at:
W Hotel New York
541 Lexington Avenue
New York, NY 10022
May 23, 2002 at 10:00 a.m.

This annual report contains certain forward-looking statements. Actual results may differ materially from those predicted herein due to certain risks and uncertainties inherent in the Company's business which are discussed on page ii of the Form 10-K.

Design
Axiom Designed Communications.
NY, LA, SLC
www.axiomdc.com

Photographer
Michael Frost Photography

Scientific Advisory Board:


InGlobe Systems Incorporated

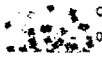
24

Emily Perret
01/07/2002 04:25 PM

To: Nicole LaForgia/ImClone@ImClone
cc: Cathleen Zicari/ImClone@ImClone
Subject: Sam needs

a paper shredder
The size of the one we have near the bathroom is good
He wants it for his office

Thank you
Emily



Cathleen Zicari
01/07/2002 04:56 PM

To: Nicole LaForgia/ImClone@ImClone
cc:
Subject: Sam needs

can you please order 2.

thx
---- Forwarded by Cathleen Zicari/ImClone on 01/07/2002 04:56 PM ----

Cathleen Zicari
01/07/2002 04:31 PM

To: Nicole LaForgia/ImClone@ImClone
cc:
Subject: Sam needs

can you please order this from varick??

thx
---- Forwarded by Cathleen Zicari/ImClone on 01/07/2002 04:31 PM ----

Emily Perret
01/07/2002 04:25 PM

To: Nicole LaForgia/ImClone@ImClone
cc: Cathleen Zicari/ImClone@ImClone
Subject: Sam needs

a paper shredder
The size of the one we have near the bathroom is good
He wants it for his office

Thank you
Emily

IMCLONE SYSTEMS INCORPORATED
Bill To: Accounts Payable, 22 Chubb Way, Somerville, NJ 08876

☐ *Ship To:*
22 Chubb Way
Branchburg Corporate Center
Somerville, NJ 08876
Telephone (908) 218-9588
Fax (908) 704-8395

☒ *Ship To:*
180 Varick Street
New York, NY 10014
Telephone (212) 645-1405
Fax (212) 645-2054

Sam please order thanks Pat

RECEIVED
JAN 15 2001

Ship To:
41A Chubb Way
Somerville, NJ 08876

P.O. Number: 4500003194
Date: 1/8/02
Vendor Name:
Department: # 136
Vendor Acct#: VARICK
Account: 630400
Phone#:
Project: 0000
Fax#:
Ordered By: NICOLE L.
Contact Name:

100888

#	Code	Item Description or Commodity Number	Catalog Number	Quantity	Quoted Unit Price	Final Unit Price	Total Price
1	A.	220 OFFICE SHREDDER.	FEL-38221	2	$479.00	~~$699.00~~ $699.00 ea	
2							
3							
4							
5							
6							
7							
8							
9							
10							

Quoted Total: Final Total $1398.00

Reason For Order: PER. 1 FOR SAM WAKSAL'S OFFICE, PER HIS OFFICE'S REQUEST. 1 FOR HWW CONFERENCE ROOM, PER HIS OFFICE'S REQUEST

Approvals
Dept. Head
COO/VP
Finance

Rush
MSDS
COA
CSA
RSA

1/15/02

Code Legend: S - Stock, D - Deliver, H - Hold, L - Lot Control

ORDER TAKEN BY: Marked 1-15-02 QUICK ORDER DUE DATE: 1-16-02

1-17-2
1-22-2

COPIES TO: PURCHASING / A/P / RECEIVING / USER

8082187764 T-801 P.002/004 F-407

Aug-13-2002 10:34am From-IMCLONE SYSTEMS

HCEC 34833
Confidential Treatment Requested

CONFIDENTIAL

O'MELVENY & MYERS LLP

LOS ANGELES
CENTURY CITY
IRVINE
MENLO PARK
NEWPORT BEACH
NEW YORK

555 13th Street, N.W.
Washington, D.C. 20004-1109

TELEPHONE (202) 383-5300
FACSIMILE (202) 383-5414
INTERNET: www.omm.com

SAN FRANCISCO
TYSONS CORNER
HONG KONG
LONDON
SHANGHAI
TOKYO

September 13, 2002

OUR FILE NUMBER
410,075-002

WRITER'S DIRECT DIAL
202-383-5374

WRITER'S E-MAIL ADDRESS
lblalack@omm.com

VIA HAND DELIVERY

Alan Slobodin, Esq.
Counsel to the Majority Staff
Subcommittee on Oversight & Investigations
House Committee on Energy and Commerce
2125 Rayburn House Office Building
U.S. House of Representatives
Washington, D.C. 20515

Dear Alan:

As you know, ImClone Systems ("ImClone") continues to produce documents responsive to the letter from Chairmen Tauzin and Greenwood, dated August 19, 2002. We are making good progress in collecting responsive documents and we expect to complete that production in the near future.

The Subcommittee's August 19, 2002, letter requested "records relating to the destruction ... of records or other information responsive to requests issued to ImClone Systems or Samuel Waksal by the SEC or the House Energy and Commerce Committee." While we do not know whether Samuel Waksal engaged in any shredding of responsive documents, the company is in possession of records relating to the purchase of shredders in early January 2002. In light of the nature of your ongoing investigation, ImClone wanted to ensure that these records were brought to your attention promptly. These records are Bates labeled HCEC 34808 through HCEC 34879.

On January 7, 2002, an assistant to Dr. Samuel Waksal sent an e-mail message to a "floater" assistant that read: "Sam needs a paper shredder. He wants it for his office." The message was copied to ImClone's office manager, who is also Dr. Harlan Waksal's administrative assistant. On the same day, the office manager sent an e-mail message to the "floater" that read: "can you please order 2. thx."

We understand that the office manager did not discuss with Dr. Harlan Waksal the initial request for a shredder or the decision that two shredders be purchased. The purchase order was

processed and the order for the shredders placed shortly thereafter. Subsequently, one of the shredders was placed in Dr. Samuel Waksal's office and the other was placed in a conference room adjacent to Dr. Harlan Waksal's office and accessible from the common hallway.

Other than any document destruction that may have occurred as described in our lawsuit against Dr. Samuel Waksal, we have no indication that any responsive documents were shredded after the shredders were delivered to the company. In particular, we understand that Dr. Harlan Waksal did not shred — nor did he direct the shredding of — any documents that were requested by the various federal entities investigating this matter, including the House Energy and Commerce Committee. In addition, we understand that Dr. Harlan Waksal is aware of no instance in which ImClone Systems employees shredded such documents. As indicated above, he played no role in the decision to purchase the shredders (other than by signing a routine purchase order, the contents of which he did not review).

On January 8, 2002, ImClone received an informal request from the Securities and Exchange Commission for certain company records. That evening, ImClone's Legal Department sent an e-mail message to department heads advising them not to "discard any documents you may have in your possession relating to the Company's BLA for Erbitux, including documents relating to communications with shareholders and analysts." On January 28, 2002 and February 1, 2002, ImClone's Legal Department distributed company-wide e-mail messages reminding all employees of the previous message and directing that additional types of documents be retained. As you know, we have previously produced those document retention directives to you.

Should you have any questions regarding this information, please contact me at your earliest convenience.

Very truly yours,

Lee Blalack/JBB

K. Lee Blalack, II
for O'MELVENY & MYERS LLP

Enclosures

cc: David Nelson, Esq. (via hand-delivery w/o enclosure)
Counsel to the Minority Staff

UNC SCHOOL OF MEDICINE

25

January 15, 2002

Dr. Sam Waksal
Dr. Harlan Waksal
Imclone Systems, Inc.
180 Varick Street
New York, NY 10014

Dear Sam and Harlan,

I am sorry there has been some turbulence and possible misunderstandings relating to the filing for approval of C225 (Erbitux). I know this must be distressing for everybody. Since many outsiders apparently are suffering from a lapse in confidence in the company as a result of the various public statements and disclosures, I suggest that your scientific advisory board could help if you were to bring us together to review the situation in some detail. I realize that I am not a cancer investigator but I think the board could be very useful at this particular time and I suggest that you do bring us together again for this purpose.

I know you are doing everything possible to get the drug filed and approved, and we are all hoping this can be done as soon as possible for the sake of the patients who need the drug.

Sincerely,

P. Frederick Sparling, MD
J. Herbert Bate Professor and Chair of Medicine and
Microbiology and Immunology, Emeritus
University of North Carolina at Chapel Hill
547 Burnett-Womack, CB# 7030
Chapel Hill, NC 27599-7030

School of Medicine • Division of Infectious Diseases • Campus Box 7030 • 547 Burnett-Womack
The University of North Carolina at Chapel Hill • Chapel Hill, NC • 27599-7030
Administrative Office: (919) 966-2536 • FAX: (919) 966-6714 • Infection Control: (919) 966-3242

26

January 18, 2002

Via Regular & Certified Mail
Return Receipt Requested

Samuel D. Waksal
150 Thompson Street, 5th Floor
New York, New York 10012

Harlan Waksal
180 Varick Street
New York, NY 10014

Re: That certain (i) Consolidated and Amended and Restated Promissory Note, dated January 15, 2002, in the original principal amount of $48,900,000 (the "Note"), executed by Samuel D. Waksal ("Borrower"), payable to the order of Bank of America, N.A. ("Bank"), (ii) Amended and Restated Pledge Agreement, dated January 15, 2002 , between the Borrower and the Bank including the Collateral Maintenance and Notice Rider attached thereto (the "Rider"), (iii) the Continuing and Unconditional Guaranty of Harlan Waksal (the "Guarantor") to the Bank, dated January 15, 2002, of the obligations of the Borrower to the Bank, including the Collateral Maintenance and Notice Rider, dated January 15, 2002, between Guarantor and the Bank (the "Guarantor Rider") and (iv) any and all other documents, instruments and agreements executed and/or delivered by Borrower or any third party in connection with the Note, including, without limitation, Promissory Notes executed and delivered by the Borrower, or guaranteed by the Borrower, to the Bank in the aggregate principal amount of $29,967,000 and a letter of credit in the amount of $500,000 issued at the request of Borrower (collectively, the "Loan Documents").

Dear Drs. Waksal:

This letter is intended to notify Borrower and Guarantor that an Event of Default has occurred under the Note due to Borrower's and Guarantor's failure to observe, perform and comply with the following provisions of the Rider and the Guarantor Rider:

Paragraph 3(b) of the Rider

Paragraph 3(b) of the Guarantor Rider

The Bank hereby declares the Note, all interest thereon and all other amounts payable under the Note and each other Loan Document to be forthwith and immediately due and payable. Commencing immediately, Bank shall have the option, at its sole discretion and without notice, to exercise all available rights and remedies under the Loan Documents, at law or in equity.

You are hereby notified that this notice and Bank's past or future failure to exercise available rights and remedies is not intended to (i) operate as a waiver of rights and remedies, or (ii) indicate any agreement on the Bank's part to forbear from exercising its rights and remedies. Further, any single or partial exercise by the Bank of any of its rights and remedies shall not preclude any other or further exercise of any available rights and remedies. The Bank is not obligated in any way with respect to future dealings between Bank and Borrower and Guarantor.

Should you have any questions concerning this matter, please contact the undersigned at (212) 407-5466.

Sincerely,

Jane R. Heller

Jane R. Heller
Senior Vice President

Book NYK 1261401

** TOTAL PAGE.04 **

CONFIDENTIAL

TABLE I — SECURITIES TO BE SOLD

Furnish the following information with respect to the acquisition of the securities to be sold and with respect to the payment of all or any part of the purchase price or other consideration therefor:

Title of the Class	Date you Acquired	Nature of Acquisition Transaction	Name of Person from Whom Acquired (If gift, also give date donor acquired)	Amount of Securities Acquired	Date of Payment	Nature of Payment

INSTRUCTIONS:

1. If the securities were purchased and full payment therefor was not made in cash at the time of purchase, explain in the table or in a note thereto the nature of the consideration given. If the consideration consisted of any note or other obligation, or if payment was made in installments describe the arrangement and state when the note or other obligation was discharged in full or the last installment paid.

2. If within two years after the acquisition of the securities the person for whose account they are to be sold had any short position, put or other option to dispose of securities referred to in paragraph (d)(3) of Rule 144, furnish full information with respect thereto.

TABLE II — SECURITIES SOLD DURING THE PAST 3 MONTHS

Furnish the following information as to all securities of the issuer sold during the past 3 months by the person for whose account the securities are to be sold

Name and Address of Seller	Title of Securities Sold	Date of Sale	Amount of Securities Sold	Gross Proceeds

REMARKS:

INSTRUCTIONS:

See the definition of "person" in paragraph (a) of Rule 144. Information is to be given not only as to the securities of the issuer proposed to be sold but also as to all other securities of the issuer purchased within the past 3 months by the person for whose account the securities are to be sold.

ATTENTION:

The person for whose account the securities to which this notice relates are to be sold hereby represents by signing this notice that he does not know any material adverse information in regard to the current and prospective operations of the issuer of the securities to be sold which has not been publicly disclosed.

DATE OF NOTICE

SIGNATURE

The notice shall be signed by the person for whose account the securities are to be sold. At least one copy of the notice shall be manually signed. Any copies not manually signed shall bear typewritten or printed signatures.

ATTENTION: Intentional misstatements or omission of facts constitute Federal Criminal Violations (See 18 U.S.C. 1001)

SEC 1147 (10-00)

Special meeting of the Board of Directors of ImClone Systems Incorporated held on January 25, 2002 27

Special meeting of the Board of Directors of ImClone Systems Incorporated was held at 180 Varick Street, New York on January 25, 2002, starting at 3:00PM. All members of the Board participated. All were present but for Mr. Barth, Dr. Ringrose and Dr. Mendelsohn who participated by telephone. Also present were Cathy Vaczy, Vice President, Legal, John B. Landes, Senior Vice President Legal who acted as the Secretary for the meeting and Daniel S. Lynch, Senior Vice President, Finance, and Chief Financial Officer. Present to represent independent Directors of the Board were members of the firm Sullivan & Cromwell, Michael Cooper and Michael Tomaino. Present to represent the Company were representatives of the firm of Davis Polk & Wardwell, Susan Merrill, John Clarke, Dennis Glazer and Phillip Mills.

The need to retain all documents was discussed including e-mails and voice mails.

Susan Merrill for Davis Polk & Wardwell spoke in detail of the examination by Davis Polk in connection with matters leading up to the Refusal to File letter. The Board then discussed these matters with management and with the representatives of Davis Polk.

The Board discussed the formation of a committee of scientists from the Board to work with management on regulatory and clinical issues including the refiling of the ERBITUX application, and agreed that Dr. DeVita, Dr. Mendelsohn, and Dr. Levine should serve on such committee of the Board and they agreed to do so.

It was reported to the Board that various forms 8-K had that day been filed with the Securities and Exchange Commission, including those which indicated that Peter Peterson had resigned from the Board, that ongoing investigations had been initiated by the Securities and Exchange Commission, Department of Justice and the US House of Representatives Committee on Energy and Commerce with respect to ImClone Systems, and of forced sales of stock of Dr. Samuel Waksal along with some of Dr. Harlan Waksal that had been offered up in guarantee of obligations of Dr. Samuel Waksal.

The Board discussed trading in shares of ImClone Systems in the months of November and December 2001 by officers and employees of ImClone Systems and authorized Davis Polk & Wardwell to investigate this matter. The Board also discussed the determination that the Company had made in the past of which officers were required to file reports of their transactions in Company shares under Section 16.

The Board then met in executive session without Messrs. S. Waksal, H. Waksal, Bodnar and Ringrose during which there was a discussion of the issues facing the Company and the appropriate process and people for dealing with those issues, including a discussion about the formation of a committee of independent directors to oversee the issues, the appropriate counsel to represent that committee and the alternatives for the management of the Company going forward. Mr. Barth raised the concern of whether Mr. Kies would be viewed as an independent Director were Sullivan and Cromwell retained and, while reiterating his full confidence in Sullivan and Cromwell's abilities, he expressed the desire that Mr. Kies remain independent. Mr. Barth and Dr. Mendelsohn cast dissenting votes on the matter of retaining Sullivan and Cromwell to represent the special committee of the Board. Following the meeting, Mr. Miller telephoned Mr. Goldhammer to change his in favor vote on this matter to a dissenting vote.

HEALTH

ImClone Directors Had Contracts With Firm Worth $112,000 a Year

By GEETA ANAND
Staff Reporter of THE WALL STREET JOURNAL

Two scientists serving on the board of ImClone Systems Inc. had scientific contracts with the biotech company that paid them together a total of $112,000 a year for three years.

Biotechnology executives and experts in corporate governance said that such arrangements, while not unheard of in the biotech world, are unusual. More commonly, scientists that are paid by companies sit on scientific advisory boards, but not on boards of directors overseeing company management.

"Somebody was not thinking through what we mean by independent directors when they signed contracts with these guys," said Jay Lorsch, a Harvard Business School professor.

John Mendelsohn, a cancer researcher who is president of the M.D. Anderson Cancer Center in Houston, didn't return calls Monday seeking comment on his $12,000-a-year contract with ImClone. Dr. Mendelsohn invented the compound that ImClone is testing as a cancer drug, but which had a major setback with the Food and Drug Administration last month.

ImClone signed the other scientific contract for $100,000 with board member Vincent Devita Jr., director of the Yale Cancer Center, according to the company's proxy for fiscal 2000. Dr. Devita couldn't be reached for comment Monday.

The company paid the two board members together a total of $112,000 in scientific contracts annually in 1998, 1999 and 2000, according to filings with the Securities and Exchange Commission.

Mr. Lorsch, who teaches corporate governance at Harvard

Business School, said ImClone's situation isn't uncommon for a new venture but is not in the best long-term interest of shareholders who need the checks and balances of an independent board.

Another director, Robert Goldhammer, is a partner in Concord International Group, a money-management firm that ImClone paid $412,000 in 2000 to manage its debt-security portfolio. Concord said Mr. Goldhammer was away and unavailable for comment.

ImClone's management and board are already under a magnifying glass. The company is under investigation by a congressional committee, SEC and Justice Department, which are raising the question of whether the company misled investors and patients about the likelihood of its cancer drug winning approval from the FDA early this year. The company's leadership made bullish statements on the drug's prospects throughout last year but then disclosed Dec. 28 that the FDA had refused to allow ImClone to file an application for approval of the colorectal-cancer drug, Erbitux.

The stock of ImClone has fallen from above $75 a share a few weeks before the FDA decision to $17.90 on the Nasdaq Stock Market Monday.

ImClone's senior management has said it was taken by surprise by the FDA's refusal letter on Dec. 28, and that it hopes the FDA's concerns can be remedied with data from its completed clinical trial. But a Washington publication, the Cancer Letter, published excerpts of the letter that suggest the FDA had substantial questions about the trial design. Some observers have questioned what senior management and ImClone's board knew of the FDA's concerns and whether the board exercised enough oversight over management to recognize the problems that the FDA raised about the design of the clinical trials for the cancer drug.

Dr. Mendelsohn has said he knew the FDA had some questions but didn't think they were make-or-break issues.

Write to Geeta Anand at geeta.anand@wsj.com

Updated January 29, 2002 12:01 a.m. EST

29

Subject: Re: Charitable contributions
Date: Fri, 08 Feb 2002 08:47:01 -0500
From: DanielL@imclone.com
To: "Kies, David M." <Kiesd@sullcrom.com>
CC: "'alevine@rockvax.rockefeller.edu'" <alevine@rockvax.rockefeller.edu>, "'andrew.bodnar@bms.com'" <andrew.bodnar@bms.com>, "'ckoob@stblaw.com'" <ckoob@stblaw.com>, "'jhkopperl@vgernet.net'" <jhkopperl@vgernet.net>, "'rbeattie@stblaw.com'" <rbeattie@stblaw.com>, "'william_r.miller@bms.com'" <william_r.miller@bms.com>

David -

Per your request, please see the attached summary of charitable contributions for affilated institutions since 1/1/99. As we recently switched computer systems, the 1999 information will need to be confirmed from the archives. I will let you know if there are any changes.

Please feel free to call me if you have any questions.

Regards,
Dan

(See attached file: charitable.xls)

Daniel S. Lynch
Senior Vice President & CFO
ImClone Systems Incorporated
180 Varick Street
New York, New York 10014
phone 646-638-5036
fax 646-638-5120
dlynch@imclone.com

"Kies, David M." <Kiesd@sullcro m.com> 02/05/2002 03:19 PM

To: "'DanielL@imclone.com'"
cc: "'jhkopperl@vgernet.net'" "'alevine@rockvax.rockefeller.edu'" "'william_r.miller@bms.com'" "'andrew.bodnar@bms.com'" "'rbeattie@stblaw.com'" "'ckoob@stblaw.com'"
Subject: Charitable contributions

HCEC 28479

Dan---
Could you please assemble and send to me a list of any charitable

Re: Charitable contributions

contributions made by the company in the past three years to M.D. Anderson, Dana Farber, Yale Cancer Center, Rockefeller University, Sloan Kettering or any other institution which has an affiliation with any of the directors that you, Sam or Harlan are aware of. My phone number is 212-558-3718 and fax is 212-558-3358. Thank you.

David

charitable.xls

Name: charitable.xls
Type: Microsoft Excel Worksheet (application/vnd.ms-excel)
Encoding: base64
Download Status: Not downloaded with message

ImClone Systems Incorporated
Charitable and Conference Support Contributions to Affiliated Institutions
For the Period 1/1/99 - Present

Affiliated Institution	Date of Contribution	Amount	Brief Desccription
Yale Cancer Center	April-01	$15,000	Annual benefit includes table of 10 and a $5,000 gift.
Yale Cancer Center	February-00	12,000	Annual benefit includes table of 10 and a $2,000 gift.
MD Anderson Cancer Center	December-01	10,000	Unrestricted educational grant for the 10th Annual Radiation Workshop being held 4/25/02-4/28/02.
MD Anderson Cancer Center	October-01	2,500	2001-2002 Annual Fund.
MD Anderson Cancer Center	March-01	10,000	54th Annual Symposium on Fundamental Cancer Research being held 10/2/01-10/5/01.
MD Anderson Cancer Center	November-00	5,000	48th Annual Meeting of the Radiation Research Society being held 4/21/01-4/25/01.
MD Anderson Cancer Center	November-00	2,500	2000-2001 Annual Fund.
MD Anderson Cancer Center	May-00	2,000	53rd Annual Symposium on Fundamental Cancer Research being held 11/14/00-11/17/00.
MD Anderson Cancer Center	January-00	25,000	52nd Annual Symposium on Fundamental Cancer Research being held 1/9/00-1/12/00.
The Rockefeller University	January-01	10,000	The Rockefeller University Annual Fund.
The Rockefeller University	May-00	5,000	Women & Science initiative to support postdoctoral fellows.
The Rockefeller University	December-99	10,000	The Rockefeller University Annual Fund.
Dana Farber Cancer Institute (Jimmy Fund)	September-01	2,500	170 mile annual bicycling event - we sponsored Paul Kopperl's son Brian. 93% of contribution goes to Dana Farber.
Dana Farber Cancer Institute (Jimmy Fund)	October-00	1,000	170 mile annual bicycling event - we sponsored Paul Kopperl's son Brian. 93% of contribution goes to Dana Farber.

Nothing payable to Sloan Kettering on a charitable basis.

UNC SCHOOL OF MEDICINE

30

February 21, 2002

Sam Waksal
Harlan Waksal
ImClone Systems
180 Varick Street
New York, NY 10014

Dear Harlan and Sam,

I have not heard from you regarding my previous suggestion that the SAB should meet to review the situation regarding the clinical trials.

I think it is advisable for me to resign from the SAB effective immediately. I am sorry to do this because we have had such a wonderful long-term relationship and I consider you my personal friends. Indeed I wish the very best for the company. I just do not believe I can be useful as a member of the SAB, and the long-term inactivity of the SAB suggests the SAB is not useful to the company.

I wish each of you the very best.

Sincerely,

P. Frederick Sparling, MD
J. Herbert Bate Professor and Chair of Medicine and
Microbiology and Immunology, Emeritus
University of North Carolina at Chapel Hill
School of Medicine
521 Burnett-Womack, CB# 7030
Chapel Hill, NC 27599-7030
Tele - 919-843-8598
Fax - 919-966-6714
Email - zman@med.unc.edu

31

ImClone CEO Returns $486,000 Profit From Possibly Rule-Breaching Stock Sales

By GEETA ANAND
Staff Reporter of THE WALL STREET JOURNAL

Samuel Waksal, chief executive of ImClone Systems Inc., has returned to ImClone about $486,000 in profit he made on some sales of company stock because he may have inadvertently breached an insider-trading regulation, a company spokesman said.

Dr. Waksal put 100,000 ImClone shares last year in an "exchange fund," which is designed to allow executives and others with concentrated stock positions to diversify stock holdings, the spokesman said. **Eaton Vance Management** of Boston operates the fund, called Altavera Capital Fund LLC.

A little over six months later, on Oct. 25, Dr. Waksal sold his stake in the fund. The fund's value had fallen, so Dr. Waksal received only 51,532 of his ImClone shares back. Four days later, he sold these shares as part of the 814,674 shares he tendered to **Bristol-Myers Squibb** Co. when that company purchased 20% of ImClone stock from existing shareholders. Dr. Waksal received $57 million from the sale of his shares as part of the $1 billion tender offer.

To discourage frequent trading by company insiders, the Securities and Exchange Commission, through a regulation known as the "short-swing profit rule," requires insiders who buy and then sell company stock within a six-month period to hand over to the company any profit made on the sale. For Dr. Waksal, the question is whether the stock he acquired from the exchange-fund withdrawal constituted a purchase.

Peter Romeo, a lawyer for Hogan & Hartson LLP in Washington who specializes in regulations on executive stock trading, said the SEC usually considers contributing stock to an exchange fund as a share disposition, and so, by extension, taking stock back out would be seen as purchasing shares.

The ImClone spokesman said, "Dr. Waksal has been advised there is no clear answer to this question under settled law," but has given ImClone a check for $486,051, the profit he made in the transaction. ImClone will hold the check until the company's board resolves the issue at an undetermined date, the spokesman said.

ImClone faces lawsuits by investors and investigations by government agencies that are reviewing, among other things, stock sales by company executives before Dec. 28, when ImClone disclosed that the Food and Drug Administration had refused to even review its cancer-drug application. ImClone hopes to get the drug back on track quickly. An Eaton Vance spokeswoman declined to comment. Also yesterday, congressional investigators broadened their inquiry into ImClone, requesting documents from several drug companies that discussed partnering with the company to produce the colorectal cancer drug Erbitux.

The House Energy and Commerce Committee sent letters to seven drug companies that sought partnership with ImClone in developing Erbitux. ImClone ultimately formed a partnership with Bristol-Myers Squibb. The committee asked for "all records including internal audits, investigations, and/or reports relating to ImClone Systems." The committee wrote to **Pharmacia** Corp., **Merck** & Co., **Eli Lilly** & Co., **Johnson & Johnson**, **Chiron** Corp., **Amgen** Inc. and **Abbott Laboratories**. A Merck representative said the company is cooperating with the committee's request. Eli Lilly said it hasn't had time to review the letter and couldn't comment. The rest of the companies couldn't be reached to comment.

—Cassell Bryan-Low and Jill Carroll contributed to this article.

WSJournal 2/22/2

1515 Holcombe Blvd.
Houston, TX 77030
Phone: 713-792-6000
Fax: 713-799-2210

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Fax

To: Catherine Vaczy, ImClone Systems, Inc.	**From:** John Mendelsohn, M.D.
Fax: 212-645-2770	**Date:** February 27, 2002
Phone:	**Pages:** 12, including cover
Re: Director's Questionnaire	**CC:**

☐ **Urgent** ☒ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

•Comments:

QUESTIONS

(1) Background Information.

(a) Please state your full name

John Mendelsohn

(b) Please indicate your date of birth

August 31, 1936

Questions and responses from Company records or prior Questionnaires. Check either "No change" or "Modify".	**If "Modify", please use this column to provide details as appropriate:**
(c) Please disclose whether you are related by blood, marriage, or adoption, not more remote than first cousin, to any director, executive officer,[1] nominee to become a director or executive officer of the Company, its parent, any subsidiary or other affiliate of the Company. The disclosure, if any, should state (for each relationship) the identity and position of such person and the nature of the relationship. Answer: ***No*** No change ___ Modify ___	
(d) Please state if you presently hold, or have held, any positions or offices with the company, its parent or any subsidiary or other affiliate of the Company. Answer: ***Director, Consultant and Member of the Scientific Advisory Board.*** No Change ___ Modify ___	Scientific Advisory Board (Consultant), Bristol-Myers Squibb (BMS).
(e) Please state whether you have been selected to serve in your present or expected capacity with the Company pursuant to any arrangement or understanding between yourself and any other person or persons (other than directors or officers of	

the Company acting solely in their capacities as such). The disclosure, if any, should describe the arrangement or understanding and include the name(s) of such person(s). Answer: *No* No change ___ Modify ___	
(f) Please disclose your business experience during the past five years (together with applicable dates). The disclosure should include your principal occupations and employment during that period and the name and principal business of any corporation or other organization in which you carried on such occupations and employment. The disclosure also should include all directorships you hold in publicly-traded corporations. Directorships in privately-held corporations, may, but need not be included. ***Note: See biography as it appears at the right. Please indicate any modifications you would like to make to it.***	**John Mendelsohn, M.D.** has been a Director of the Company since February 1998. He has served as the President of M.D. Anderson Cancer Center, University of Texas, where he has also been Professor of Medicine since 1996. From 1985 to 1996 he was Chairman of the Department of Medicine at Sloan Kettering, New York, as well as holder of the Winthrop Rockefeller Chair in Medical Oncology at Sloan Kettering. He was also Professor and Vice-Chairman of Medicine at Cornell University Medical College and an attending physician at both Memorial and New York Hospitals. Dr. Mendelsohn served on the faculty of the University of California, San Diego and was instrumental in the creation of the University's Cancer Center, where he served as Director from 1976 to 1985. Dr. Mendelsohn's work has focused on growth factors and their role in regulating the proliferation of cancer cells through cell surface receptors. Dr. Mendelsohn was responsible for developing specific monoclonal antibodies that block receptors, including epidermal growth factor receptors, which mediate growth factor activation of cell growth and division. Dr. Mendelsohn is currently a board member of Enron Corp., ~~the Richard Lounsbery Foundation~~ and the Greater Houston Partnership, and a fellow of the New York Academy of Medicine. In 1997, Dr. Mendelsohn was elected to the Institute of Medicine of the National Academy of Sciences. Note deletion

(g) Please state whether there are any committees of the Company's Board of Directors on which you serve. Answer: ***Member of the Research Oversight Committee; and the Special Committee formed in February 2002.*** No change ___ Modify ___	
2. Material Relationships and Transactions.	
(a) Please state whether there have been any transactions, or series of similar transactions, since January 1, 2001, or any currently proposed transaction, or series of similar transactions, to which the Company or any of its subsidiaries was or is to be a party, in which the amount involved exceeds $60,000 and in which you, any associate[2] of yours or member of your immediate family[3] had, or will have, a direct or indirect material[4] interest. Answer: ***No*** No change ___ Modify ___	Sold stock options to BMS October, 2001. Value approximately $6.3M.
(b) Please state whether you have been at any time since January 1, 2001, an executive officer, director or employee of, or owned of record or beneficially in excess of 10 percent of the equity interest in, any firm, corporation or other business or professional entity: (i) which has made since January 1, 2001, payments to the Company or any of its subsidiaries for property or services in excess of $70,0000 or proposes to make such payments. Answer: ***No*** No change ___ Modify ___	

(ii) to which the Company or its subsidiaries has made since January 1, 2001, payments for property or services in excess of five percent of the other entity's consolidated gross revenue for its last fiscal year or proposes to make such payments. Answer: ***No, except for any payments relating to clinical trials conducted at MD Anderson.*** No change ___ Modify ___	
(iii) to which the Company or any of its subsidiaries was indebted at any time since January 1, 2001 in an aggregate amount in excess of $18,000,000. Answer: ***None.*** No change ___ Modify ___	
(c) Please state whether you have been at any time since January 1, 2001: (i) a member of, or of counsel to, a law firm that the Company retained since January 1, 2001.[6] Answer: ***No*** No change ___ Modify ___	
(ii) a partner or executive officer of any investment banking firm that has performed services for the Company or any of its subsidiaries, other than as a participating underwriter in a syndicate, since January 1, 2001.[7] Answer: ***No*** No change ___ Modify ___	
(d) Please state whether you have had any relationship with the Company or its management (other than your	

position as a director or officer) which is substantially similar in nature and scope to those relationships listed in b. and c. above. Answer: *No* No change ___ Modify ___	
(e) Do you, any members of your immediate family or any of your associates[2] have any interest, direct or indirect, in the appointment of KPMG LLP as the Company's independent public accountants? Answer: *No* No change ___ Modify ___	
3. **Legal Proceedings.** (a) Please state whether, during the past five years, including any events occurring longer than five years ago if any development relating to such event has occurred during the past five years, (i) any petition under the Federal bankruptcy laws or any State insolvency law has been filed by or against you, or any receiver, fiscal agent or similar officer been appointed by a court for the business or property of you, any partnership in which you were a general partner at or within two years before such filing, or any corporation or business association of which you were an executive officer at or within two years before such filing	See below Yes ___ No ___ If the answer is Yes, please describe such event or events, giving dates, the name of the court and jurisdiction and other pertinent information. Enron Corp. entered Chapter 11 bankruptcy on December 2, 2001. I am a Director, not an Officer, of Enron. Site is U.S. Bankruptcy Court for the Southern District of New York.

(ii) you have been convicted in a criminal proceeding, or have been named a subject of a criminal proceeding which is presently pending (excluding traffic violations and other minor offenses).	Yes _____ No X If the answer is Yes, please describe such event or events, giving dates, the name of the court and jurisdiction and other pertinent information.
(iii) you have been the subject of any court order, judgment or decree, not subsequently reversed, suspended or vacated, which permanently or temporarily enjoined, or otherwise limited, you from any of the following activities: (A) acting as a futures commission merchant, introducing broker, commodity trading adviser, commodity pool operator, floor broker, leverage transaction merchant, any other person regulated by the Commodity Futures Trading Commission, or an associated person[2] of any of the foregoing, or as an investment adviser, underwriter, broker or dealer in securities, or as an affiliated person, director or employee of any investment company, bank, savings and loan association or insurance company, or engaging in or continuing any conduct or practice in connection with such activities.	Yes _____ No X If the answer is Yes, please describe such event or events, giving dates, the name of the court and jurisdiction and other pertinent information
(B) engaging in any type of business practice.	Yes _____ No X If the answer is Yes, please describe such event or events, giving dates, the name of the court and jurisdiction and other pertinent information.

(C) engaging in any activity in connection with the purchase or sale of any security or commodity or in connection with any violation of Federal or State securities laws or Federal commodities laws.	Yes _____ No X If the answer is Yes, please describe such event or events, giving dates, the name of the court and jurisdiction and other pertinent information.
(iv) you have been the subject of any order, judgment or decree, not subsequently reversed, suspended or vacated, of any Federal or State authority barring, suspending or otherwise limiting for more than 60 days your right to engage in any of the activities described in (A) above or your right to be associated with persons engaged in any of such activities.	Yes _____ No X If the answer is Yes, please describe such event or events, giving dates, the name of the court and jurisdiction and other pertinent information.
(v) you have been found by a court in a civil action or by the Securities and Exchange Commission to have violated any Federal or State securities law, where such judgment or finding has not subsequently been reversed, suspended or vacated, or are presently the subject of any investigation by the Securities and Exchange Commission which could result in the finding of such a violation.	Yes _____ No X If the answer is Yes, please describe such event or events, giving dates, the name of the court and jurisdiction and other pertinent information. The SEC is currently investigating matters related to Enron Corp. (in the matter of Enron Corp. HO-9350). I have been asked to provide information to the SEC, but have not been informed I am the subject of any investigation.

(vi) you have been found by a court in a civil action or by the Commodities Futures Trading Commission to have violated any Federal commodities law, where such judgment or finding has not been subsequently reversed, suspended or vacated or are presently the subject of any investigation by the Commodities Futures Trading Commission which could result in the finding of such a violation.	Yes _____ No _X_ If the answer is Yes, please describe such event or events, giving dates, the name of the court and jurisdiction and other pertinent information.
(vii) you know of any pending or contemplated legal proceedings, including administrative proceedings and investigations by governmental authorities, in which you, any associate[2] of yours, or any affiliate of the Company is or may be a party adverse to the Company, or any subsidiary or in which either you, any associate of yours, or any affiliate of the Company has or may have a material interest adverse to the Company or any subsidiary.	Yes _____ No _X_ If the answer is Yes, please describe such proceeding or investigation and other pertinent information.
4. **Ownership.** (a) Please state whether there are any equity securities of the Company which were beneficially owned[10] on February 20, 2002, by (i) you, (ii) your spouse, (iii) your minor children (iv) any other relative of yours or of your spouse who shares your home (naming such relative) and (v) any other associate[2] of yours (naming such associate[2]). The disclosure, if any, should indicate the amount of equity securities which were beneficially owned[10], which any of you have a right to acquire within 60 days after February 20, 2002, and as to which you have sole voting power, shared voting power, sole investment power or shared investment power.[11] Answer: ***Please see information at right*** No change ____ Modify ____	***Directors & Officers - Beneficial Ownership as of February 20, 2002:*** ***For: John Mendelsohn*** ***Shares of Common Stock: 0*** ***Vested Options and Warrants: 373,226***

(b) Please state whether you wish to disclaim beneficial ownership of any of the shares referenced in 4(a) above. Answer: *No* No change ___ Modify ___	
(c) Please state whether there are any persons, including any group of persons,[12] known by you to own beneficially more than 5% of the Company's common stock (or other class of voting securities). Answer: ***None other than as may be disclosed in public filings.*** No change ___ Modify ___	
(d) Please state whether you know of any arrangements,[13] including any pledge by any person of securities of the Company or any of its parents, the operation of which may at a subsequent date result in a change in control[9] of the Company. This disclosure does not require a description of ordinary default provisions contained in the Company's charter, trust indentures or other governing instruments relating to securities of the Company. Answer: ***None other than (i) in accordance with the terms of various agreements between ImClone, Bristol-Myers Squibb Company and its subsidiaries, dated as of September 19, 2001 and (ii) Hart Scott Rodino Act filing by Carl Ichan.*** No change ___ Modify ___	

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(e) Please state whether you knew of any voting trust or similar agreement or arrangement[1,3] under which more than 5% of the Company's outstanding voting securities is held or is to be held. The disclosure, if any, should describe, in each case, the amount held or to be held pursuant to the trust or agreement, its duration, the names and addresses of the voting trustees, and their voting rights and other powers under the trust or agreement. Answer: *None other than (i) in accordance with the terms of various agreements between ImClone, Bristol-Myers Squibb Company and its subsidiaries, dated as of September 19, 2001 and (ii) Hart Scott Rodino Act filing by Carl Ichan.* No change ____ Modify ____	
(f) Please confirm that you have advised the Company of any and all acquisitions and dispositions made by you during 2001 (excluding option or warrant exercises) of the Company's securities so that a Form 3, 4 or 5 could be filed with the SEC on your behalf. Yes *X* No ____	

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ImClone Systems Incorporated

Special Meeting of the Compensation and Stock Option Committee
of the Board of Directors

March 19, 2002

A special meeting of the Compensation and Stock Option Committee of the Board of Directors (the "Committee") of ImClone Systems Incorporated (the "Company") was held pursuant to notice duly given via teleconference at 1:30 p.m. on March 19, 2002.

Participating in the meeting via teleconference were the following members of the Committee: Robert F. Goldhammer (Chairman), David M. Kies, Richard Barth and Paul B. Kopperl. Dr. Peter S. Ringrose was unable to attend. Also present and participating from the Company's offices at 180 Varick Street, New York, New York 10014 were Daniel S. Lynch, the Company's Senior Vice President and Chief Financial Officer, Catherine M. Vaczy, the Company's Vice President, Legal and Associate General Counsel and Clifford R. Saffron, the Company's Vice President, Legal and Special General Counsel. Also participating via teleconference were Charles Koob of Simpson Thacher and Bartlett, counsel to the outside directors and Daniel Ryterband and Wendy Hilburn of F. W. Cook & Company, compensation consultants to the Company. A copy of the Agenda for the meeting is attached as *Attachment A* hereto. Mr. Goldhammer acted as Chairman of the meeting and Ms. Vaczy act as Secretary.

Mr. Goldhammer opened the meeting by requesting that Mr. Lynch take the participants through the meeting Agenda. Accordingly, the first item, review of the payment of bonuses to Samuel Waksal and Harlan Waksal under their employment agreements with the Company, was discussed. After due discussion of the matter by the members, it was concluded that the matter be resolved at a later date by either the Committee or the full Board after consulting with Davis Polk & Wardwell, Company counsel, and Simpson Thacher & Bartlett, independent director counsel, with respect to interpretation of the employment agreements and related matters.

Mr. Lynch then turned the meeting over to Daniel Ryterband to present a new equity plan proposal for the Company that, if approved by the Committee and the Board, would be submitted to shareholders for their vote at the Company's upcoming annual meeting of stockholders. Mr. Ryterband's presentation included a comparison of the Company's option overhang to industry peers, the fact that any proposal would need to include provisions considered friendly to shareholders and other relevant considerations. After a full discussion of the matter, the Committee authorized management to go forward with an option plan reserving 3,300,000 shares of common stock, subject to Board approval of such a plan and management's determination to its satisfaction that certain shareholders would support such a plan.

At this juncture, Mr. Ryterband and Ms. Hilburn left the meeting.

Next, the issue of Board cash compensation for 2002 was raised. It was noted that at t August 2, 2001 meeting of the Committee, raising cash compensation for the Board, except t Chairman whose would remain unchanged, was approved. The Committee determined that th appropriateness of such an increase should be put before the full Board at the next meeting of the Board.

Next, the fact that the composition of the Committee does not comply with Section 16(b) of the Securities Exchange Act of 1934, as amended (the "Exchange Act") and Section 162(m) of the Internal Revenue Code, as amended was discussed. It was discussed that the result of non-compliance under Section 16(b) is that option grants are not exempt from Section 16(b) and the result of non-compliance under Section 162(m) is that the Company is limited in certain circumstances from taking deductions for executive compensation. The failure to comply relates to Mr. Goldhammer's receipt of $150,000 in fees as Chairman of the Board and Dr. Ringrose's relationship to Bristol-Myers Squibb ("BMS"). It was noted that at the March 4, 2002 meeting of the Board, Phillip Mills of Davis Polk & Wardwell had noted that BMS' counsel had agreed with the conclusion as it relates to Dr. Ringrose, and agreed, on behalf of BMS, that Dr. Ringrose no longer serve on the Committee. Dr. Ringrose was accordingly removed from the Committee. It was determined that Mr. Goldhammer would remain on the Committee for the time being, but would discuss the possibility of successorship with William R. Miller. The Committee also discussed approving "performance goals" for the five most highly compensated individuals in the Company in order for cash compensation to comply with 162(m) and the Committee approved general performance goals.

The Committee then discussed the possibility of amending terms relating to the pricing mechanism and offering period under the Company's 1998 Employee Stock Purchase Plan. The Committee requested a presentation relating to norms in the industry for these types of plans, including an analysis of the tax treatment. It was determined that such a presentation would occur at a later date in connection with other changes to the Company's equity compensation practices.

The Committee then discussed the Report of the Compensation Committee that is required to appear in the 2001 Proxy Statement and determined that a final report would be adopted at the Committee's April 3rd meeting.

Drafts of meetings of the Committee of August 2, 2001 and November 15, 2001 were then reviewed and approved subject to any minor comments that may be provided by Committee members.

There being no further business to come before the Committee, a motion to adjourn the meeting was made, seconded and so voted and the meeting was declared adjourned.

A true and accurate record.

Attest: _____
Catherine M. Vaczy, Secretary

Attachment A

COMPENSATION AND STOCK OPTION COMMITTEE
TELECONFERENCE AGENDA
March 19, 2002, 1:30 p.m.

IMCLONE SYSTEMS INCORPORATED

---

1. Review payment of bonuses to Samuel D. Waksal and Harlan Waksal under Employment Agreements;

2. Review and discuss:
   (i) implementation of ImClone Systems Incorporated 2002 Stock Option Plan; and
   (ii) proposed amendments to the ImClone Systems Incorporated 1998 Employee Stock Purchase Plan;

3. Review composition of Compensation and Stock Option Committee as currently configured under Rule 16b-3 and 162(m);

4. Review draft of Compensation and Stock Option Committee Report to be included in Proxy Statement for 2001 fiscal year;

5. Review Committee minutes from August 2, 2002 meeting and November 15, 2002 meeting;

6. Other business, if any.

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ImClone Systems Incorporated

DR. HARLAN W. WAKSAL
EXECUTIVE VICE PRESIDENT
CHIEF OPERATING OFFICER

25, March 2002

UNC at Chapel Hill School of Medicine
Division of Infectious Disease
547 Burnett-Womack, Campus Box #7030
Chapel Hill, NC 27599-7030

Dear Fred:

I was sad to receive your letter and inclination to resign the SAB. Your relationship with ImClone has represented an important part of our core beginning.

Over the last three months the company has suffered a set back and we have been in a state of crisis management. Part of the current activities involves revitalization of the SAB. I would like to ask you to reconsider your resignation until we have an opportunity to pull ourselves back together and revisit the SAB role and address the long-term inactivity.

If you feel the recent events leave you in a position where resignation is advisable I certainly understand. As you know I have great respect for all of your scientific activities and I cherish our friendship.

Whatever you decide, please keep in touch.

Sincerely,

Harlan

180 VARICK STREET, NEW YORK, NEW YORK 10014 TELEPHONE: (646) 638-5055 FAX: (212) 691-9351

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: March 25, 2002

From: Sharon Sickafuse OTRR/DARP

Subject: February 26, 2002, meeting with ImClone regarding the 12-28-02 RTF letter issued to their BLA for Cetuximab

To: Attendees
IND 5804

ImClone gave a brief slide presentation of their plans and proposals for addressing the issues in the RTF letter (see Appendix 1). Included in the presentation was an overview of the work efforts to date. This was followed by an overhead presentation by the FDA (see Appendix 2) of FDA's responses to ImClone's questions submitted by facsimile on February 25, 2002 (hard copy is amendment 287).

The following captures the discussion that occurred during the FDA's presentation:

- The FDA clearly stated to ImClone that reanalysis of the data from CP02-9923 will not be sufficient to address the deficiencies in this application. This conclusion is based upon a determination that there are significant design and conduct flaws in the study that cannot be fully addressed by sending missing data. Data from an additional trial or trials that are adequate and well-controlled are necessary.

- The FDA agrees that a proposal to collect additional data and conduct a reanalysis of CP02-9923 may make the data more useful. However, FDA cannot concur with the adequacy of the plan until it has been submitted for review. ImClone was advised to submit a detailed reanalysis plan including the IRAC reread procedure to the IND for review and comment. Following FDA review, FDA will have a telephone conference with ImClone to provide comments on the specific plan.

- The FDA explained its position regarding the need for information about whether the use of iriniotecan is needed in conjunction with Cetuximab. If the combination at some point has been shown to represent a substantial advance over available therapy and to have acceptable toxicity, ImClone may receive a license for Cetuximab for use in combination with irinotecan based upon sufficient information regarding the contribution of irinotecan to support labeling for the combination. While the best way to provide such information would be a trial showing that Cetuximab plus irinotecan is superior to Cetuximab alone, there is not an absolute requirement for such a trial for licensure. In some cases, the need for both agents of a combination may be established based upon mechanistic arguments and/or animal data. In this case, however, as noted in the past, the Agency stated that it has not found the animal data and mechanistic arguments submitted convincing and the clinical data to date do not support the argument of an absolute need for irinotecan. Additionally, the Agency pointed out that irinotecan has substantial toxicity and its use in irinotecan resistant patients as proposed

by ImClone should be supported by strong evidence. Depending on the details of its design and results, study EMR-007, while not adequately powered to detect clinically important differences between monotherapy and the combination, may address this concern adequately for licensing in one of two ways. It may establish the safety and efficacy of Cetuximab monotherapy; or, it may, though not providing the need for irinotecan, provide sufficient supportive information in conjunction with mechanistic and animal data to be submitted, to support labeling for use of the combination. In such a case, theAagency may request further evaluation of the need for irinotecan in the combination as a post-marketing commitment.

- Regarding ImClone's proposal to provide data from a randomized, Phase 2, European study (EMR-007), conducted by Merck, which compares Cetuximab plus irinotecan to Cetuximab alone, FDA stated that based on the protocol synopsis that ImClone provided (by facsimile on February 21, 2002, with hard copy also submitted on that date), EMR-007 has the potential to be used in conjunction with CP02-9923 and CP02-0141 in support of licensure. However, FDA has not reviewed the complete protocol and the statistical analysis plan as the protocol was just received on February 25, 2002. Following FDA review, FDA will have a telephone conference with ImClone to provide comments on the adequacy of the trial and comments on the statistical analysis plan. FDA recognizes that any comments cannot be used to alter the protocol design because, as noted by Merck, EMR-007 will finish accruing patients in a couple of weeks, however comments on the sample size and utility of expansion of the trial will be conveyed.

- ImClone was advised that, depending on the results of EMR-007, they may need to provide data from additional studies.

- ImClone clarified that the same EGFR expression assay (manufactured by DAKO) that was used in the U.S. studies is being used in the EMR-007 study. In addition, product used in the EMR-007 study is from ImClone's pilot plant.

- Data correlating the dose selected with clinical outcome and tumor saturation is necessary for filing the BLA.

Action Items for ImClone:

1. Submit to the IND the detailed plan for reanalysis of CP02-9923 and CP02-0141, including the IRAC reread procedure. Schedule a telephone conference to discuss the plan with FDA after FDA review.

2. Submit to the IND the results from the reanalysis of CP02-9923 and CP02-0141.

3. Submit to the IND the complete Merck protocol EMR-007 and the statistical analysis plan for review. (Update: protocol EMR-007 was submitted to IND 5804 on February 21, 2002 and received on February 25, 2002. A telephone conference regarding this submission was held on March 1, 2002).

4. Submit to the IND an outline of the preclinical and clinical information that you have to support the synergistic effect of Cetuximab and irinotecan for irinotecan-refractory disease..

Appendix 1: Slide Presentation by ImClone
Appendix 2: Overhead Presentation by Dr. Patricia Keegan, CBER

Attendees

Center for Biologics Evaluation and Research

Office of the Commissioner
Patty Delaney, Office of Special Health Issues

Office of Therapeutics Research and Review
Jay Siegel, M.D.

Division of Application Review and Policy
Glen Jones, Ph.D.
Sharon Sickafuse, M.S.

Division of Biostatistics
Ghanshyam Gupta, Ph.D.

Division of Clinical Trial Design and Analysis
Martin Green, Ph.D.
Susan Jerian, M.D.
Patrica Keegan, M.D.
George Mills, M.D.
Lee Pai-Scherf, M.D.
Mercedes Serabian, M.S.

Division of Monoclonal Antibodies
Chana Fuchs, Ph.D.
Kathyrn Stein, Ph.D.
Keith Webber, Ph.D.

ImClone Systems, Incorporated
Nozar Azarnia, Ph.D., Senior Director, Biostatistics
Lily Lee, Ph.D., V.P., Regulatory Affairs and Biostatistics
Nikhil Mehta, Assistant V.P., Regulatory Affairs
Michael Needle, M.D., V.P., Clinical Affairs
Joe Tarnowski, Ph.D., V.P., Manufacturing
Harlan Waksal, M.D., Executive V.P. and Chief Operating Officer
Sam Waksal, Ph.D., President and Chief Executive Officer

ImClone's Invited Observers

Bristol Myers Squibb
Andrew Bodnar, M.D., V.P., Medical and External Affairs
Laurie Smaldone, M.D., Senior V.P., Global Regulatory Science

Merck KgaA
Angus Grant, Ph.D., Director, Regulatory Affairs

Marti Nelson Cancer Research Foundation
Robert Erwin, Director

3-4-02; finalized 3-25-02

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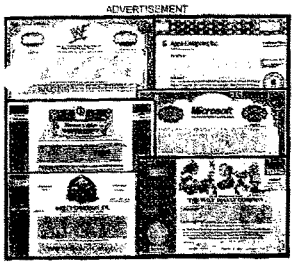
Tuesday March 26, 6:04 pm Eastern Time

Related Quote
IMCL 24.43 -0.20
delayed 20 mins - disclaimer
Quote Data provided by Reuters

ImClone's CEO violates SEC rules with stock filing

By Toni Clarke

NEW YORK, March 26 (Reuters) - ImClone Systems Inc. (NasdaqNM:IMCL - news) Chief Executive Samuel Waksal could face tens of thousands of dollars in fines after failing to report certain stock trades to regulators within the legal time frame, lawyers said.



In February, Waksal notified the Securities and Exchange Commission for the first time of 50 trades he made in ImClone stock going back as far as 1992, transactions that should have been reported within months of their execution.

Waksal listed the trades in a Form 5 document at the same time he repaid nearly $500,000 in profit from trading ImClone shares in violation of an SEC rule that prohibits insiders from profiting from shares bought and sold within six months.

Securities lawyers said the regulatory agency, which presses charges against executives for violating filing deadlines only a couple times a year, could fine Waksal as much as $100,000.

"He's in very dangerous territory," said Peter Romeo, a lawyer who specializes in insider trading at Hogan & Hartson LLP. "I'd like to know if I was the SEC why some of these filings are 10 years late."

ImClone officials declined to comment on the delay. Waksal and his brother, Harlan, the company's chief operating officer, are under investigation by the SEC for possible irregular share sales ahead of the purchase of a 20 percent stake in ImClone by drug company Bristol-Myers Squibb Co.'s last year.

Earlier this month, the House Energy and Commerce Committee, which is looking into allegations the company misled investors about the prospects for its experimental cancer drug, Erbitux, asked Samuel Waksal to provide it with details of trading in ImClone stock by members of his family.

The request followed a disclosure that his daughter, Aliza Waksal, sold nearly $2.5 million of ImClone stock on Dec. 27, a day before the company revealed the U.S. Food and Drug Administration had declined to review an experimental cancer drug. The FDA said clinical trials of the drug Erbitux were flawed and that it needed additional information.

DETAILS OF TRADES

The trades Waksal reported in the Form 5 document, filed Feb. 14, detail a mixture of acquisitions, sales and gifts since 1992. On Sept. 1, Waksal acquired 1.2 million options to buy ImClone stock at $50 a share. On Oct. 29, he sold 814,674 shares to Bristol-Myers for $70 a share.

John Heine, a SEC spokesman, said corporate officers and directors, as well as investors holding 10 percent or more of a company's stock, are obliged to file a Form 4 if there is a change in their holdings. The form is due within 10 days of the close of the month in which the transaction took place.

Form 5, Heine said, can be used in certain situations by people who forget to file a Form 4. But even a Form 5 must be filed within 45 days of the end of the company's fiscal year.

Brian Lane, a lawyer who specializes in securities law at Gibson Dunn & Crutcher, said sanctions for late filings vary from a warning to hefty fines. The SEC, which is seeking the ability to fine companies directly, must take companies to court to levy the fine.

ImClone's shares have risen 81 percent to $25 from a two-year low of $13.77 on Feb. 8 as investors regain confidence that Erbitux will reach market, albeit later than anticipated. The company's shares on Dec. 6 traded as high as $75.45 amid optimism the drug would win early approval by the FDA.

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RICHARD BARTH
823 EUCLID
HOUSTON, TEXAS 77006

March 28, 2002

Dear Mr. Goldhammer,

This is to confirm my telephone advice to you following the meeting of Independent Directors of March 25, 2002 that I will not stand for re-election to the Board.

Under the circumstances I do not consider it appropriate to continue as a director. Accordingly I will resign from the Board after I have had the opportunity to vote on the minutes of the March 25, 2002 meeting, which need to reflect my position & dissent from the Board's action, as well as on the minutes of the meetings of March 21 and 23 of the Independent Directors.

Yours truly,

Richard Barth

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3/29/02 WSJ

ImClone CEO's Transaction Reports Are Late

NEW YORK (Reuters)—ImClone Systems Inc. Chief Executive Samuel Waksal notified the Securities and Exchange Commission last month for the first time of 50 trades he made in ImClone stock going back as far as 1992, transactions that should have been reported within months of their execution.

Dr. Waksal listed the trades in a regulatory filing at the same time he repaid nearly $500,000 in profit from trading ImClone shares in violation of an SEC rule that prohibits insiders from profiting from shares bought and sold within six months.

Securities lawyers said the SEC, which has at times pressed charges against executives for violating filing deadlines only a couple of times a year, could fine Waksal as much as $100,000. "I'd like to know if I was the SEC why some of these filings are 10 years late," said Peter Romeo, a lawyer at Hogan & Hartson LLP who specializes in insider trading.

ImClone officials declined to comment on the delay. Regulators in December declined to accept ImClone's application for approval of Erbitux, a drug candidate for cancer. ImClone and its partner, Bristol-Myers Squibb, which owns about 20% of ImClone, are seeking to resubmit the application with new data. Regulators and a congressional committee have been seeking to determine whether ImClone misled investors about the prospects for the drug, and whether any improper trading occurred before the company disclosed the setback to Erbitux.

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ImClone Systems Incorporated

Regular Meeting of the Board of Directors

March 29, 1999

A regular meeting of the Board of Directors of ImClone Systems Incorporated (the "Company") was held pursuant to notice duly given at the Company's principal executive offices at 180 Varick Street, New York, New York 10014 beginning at 10:00 a.m. on March 29, 1999. Present at the meeting were the following members of the Board of Directors: Jean Carvais, Vincent T. DeVita, Jr., Robert F. Goldhammer (Chairman), David M. Kies, Paul B. Kopperl, William R. Miller, Samuel D. Waksal and Harlan W. Waksal. Richard Barth participated by telephone. Dr. John Mendelsohn was unable to attend. Also present were John B. Landes, the Company's General Counsel and Carl S. Goldfischer, Vice President, Finance and Chief Financial Officer. Mr. Goldhammer served as Chairman of the meeting and Mr. Landes served as Secretary of the meeting.

The first order of business was the unanimous approval by the Board of the minutes of the previous Board meeting held on January 25, 1999, a draft of which had been provided to the members of the Board. These were approved, with suggestions for language changes by Paul Kopperl, which have been incorporated.

Dr. Harlan Waksal discussed with the Board the present status of the Company's research and development operations. First in connection with the Company's research efforts, Dr. Waksal stated that outside researchers collaborating with the Company continue to experiment with ImClone's IL-6 mutein in liver repair, and are finding interesting results which the Company continues to monitor.

In the area of cancer vaccines, the Company is conducting several projects as well as preparing its melanosomal antigen gp75 for clinical trials. Dr. Waksal related to the Board that the work on the gp75 project included the Company's efforts to choose an appropriate delivery vehicle for the antigen, possibly from a third party.

Dr. Waksal described the current status of the planned Phase III clinical trial of C225 combined with radiation tested against radiation alone in head and neck patients. He told the Board that the first patient was to be enrolled shortly. He described the targeted breadth and duration of this trial. He described the same for an additional planned Phase III trial of C225 combined with chemotherapy tested against chemotherapy alone also in head and neck cancer patients, that is to be conducted with the Eastern Cooperative Oncology Group (ECOG). He also described the pending Phase II study in which C225 would be used in combination with chemotherapy in refractory patients, i.e., patients who had been treated with chemotherapy and whose cancer had progressed.

Various additional Phase II C225 studies planned by the Company's clinical group were also described.

Management discussed with the Board the status of manufacturing of C225, including process and product development by Boehringer Ingelheim Pharma KG in Germany. Management discussed with the Board its plans in response to limited availability of a critical nutrient in the manufacturing process.

Dr. Waksal discussed with the Board the status of a pre-clinical program with the Company's anti-KDR antibody for inhibition of angiogenesis, including the status of efforts to produce the antibody in sufficient quantities to support clinical trials of the antibody intended to start in 1999.

Management discussed with the Board various senior level positions that the Company was seeking to fill in connection with regulatory, medical affairs and manufacturing.

Dr. Samuel Waksal then described to the Board the Company's current efforts in business development. He indicated that the Company was continuing to take a conservative approach to partnering in its anti-angiogenesis program, and would continue to independently move this program forward toward clinical trials of the chosen antibody candidate and to support its small molecule discovery program in this area.

Question was raised by the Board relative to the Company's ongoing plans for commercialization of C225 in North America. Dr. Waksal indicated that all avenues, including those of potentially working with third parties, needed to be evaluated closely.

Dr. Sam Waksal discussed with the Board the possibility of a limited equity financing through the sale of common stock during 1999 as part of a longer term financing strategy for the Company.

Dr. Waksal then told the Board that Dr. Carl Goldfischer was intending to leave the employ of the Company shortly after the coming shareholders meeting to return to investment banking, and expressed his appreciation on behalf of the Company for Carl's efforts on the Company's behalf during the three years that he had served the Company.

Paul Goldstein, controller for the Company, presented the 1999 operating budget to the Board, outlining areas in which revenues and expenses would differ from those of prior years. The Board discussed with management the revenue assumptions, in particular those to be derived under the recently signed C225 based agreement between the Company and Merck KGaA. It also discussed certain budgeted expense increases over prior years, including an expanded number of manufacturing runs of C225 at the Branchburg facility, a number of runs of clinical material under the Research and Development agreement with Boehringer Ingelheim Pharma KG, as well as the expanded set of clinical trials for C225.

The Board strongly encouraged the Company in the future to complete presentations of the budget to the Board earlier in the cycle.

Ron Martell, VP of Marketing, was asked to join the meeting, and Mr. Martell presented to the Board the plans for the commercial manufacturing facility for the production of C225. The Board discussed with management different possible production concepts that were being considered by the Company and its partner Merck KGaA. Mr. Martell indicated that the Company had done a careful evaluation of potential cost differentials that could result from location of the planned facility at alternative sites nationwide and of various operational factors that would influence this decision. Mr. Martell indicated that based on this extensive evaluation, results from which had been shared with Merck, management had made a decision to locate the commercial manufacturing facility in New Jersey, adjacent to its current pilot manufacturing facility. Mr. Martell also described to the Board the status of the ongoing discussions with Merck called for in the C225 agreement concerning the production concept and manufacturing line of credit due from Merck to support the buildout.

The Board addressed the issue of a potential Board seat for an individual from Merck KGaA, as per the terms of a two party signed letter of December 15, 1997 between the Company and Merck. The designee of Merck included in that letter, Edward R. Roberts, having retired from Merck, it was determined unanimously by the Board that the present chief executive officer of Merck, Bernhard Scheuble, should be invited to join the Board and for that purpose the size of the Board should be increased from 10 members to 11 members.

The Board then turned to the following new business matters: (i) the approval of the granting of options to each of Sam Waksal and Harlan Waksal, which grants had been approved by the Compensation and Stock Option Committee (the "Compensation Committee") on March 12, 1999, subject to Board approval, shareholder approval and the receipt of a favorable opinion from F.W. Cook and Company, an unaffiliated executive compensation consulting firm; (ii) the amendment of the 1998 Employee Stock Purchase Plan (the "Stock Purchase Plan"); and (iii) the approval of 1998 annual meeting items. After due discussion of each matter, the Board unanimously adopted each of the following resolutions:

Option Grants to Sam Waksal and Harlan Waksal–

> RESOLVED, that subject to shareholder approval, the receipt of a favorable opinion from F.W. Cook and Company, an unaffiliated executive compensation consulting firm, and based on those considerations set forth in Attachment A hereto, an option to purchase 1,000,000 shares of the Company's common stock, $.001 par value (the "Common Stock"), is hereby granted to Samuel D. Waksal on the terms set forth in Attachment A; and it is further

RESOLVED, that subject to shareholder approval, the receipt of a favorable opinion from F.W. Cook and Company, an unaffiliated executive compensation consulting firm, and based on those considerations set forth in Attachment B hereto, an option to purchase 650,000 shares of the Company's Common Stock is hereby granted to Harlan W. Waksal, on the terms set forth in Attachment B; and it is further

Amendment of Stock Purchase Plan -

RESOLVED, that Section 3(a) of the Stock Purchase Plan is hereby amended to eliminate the requirement that an employee be employed by the Company for a minimum period of six months before becoming eligible to participate in the Stock Purchase Plan and that Section 3(a) of the Stock Purchase Plan accordingly read in its entirety as follows:

"Options may be granted only to employees of the Company or an Affiliate. An employee of the Company or any Affiliate shall be eligible to participate in the Plan upon commencement of employment with the Company; provided, that no employee of the Company or any Affiliate shall be eligible to be granted an Option under the Plan, unless, on the Offering Date of such Offering Period, such employee's customary employment with the Company or such Affiliate is at least twenty (20) hours per week and at least five (5) months per calendar year."

and it is further

Annual Meeting –

General -

RESOLVED, that a representative of the Company's transfer agent, EquiServe, is hereby authorized to act as inspector of election at the Annual Meeting of Stockholders to be held on May 24, 1999 (the "Annual Meeting"); and it is further

RESOLVED, that Samuel D. Waksal, Robert F. Goldhammer and John B. Landes are hereby authorized to act as proxies at the Annual Meeting; and it is further

Nominees for Director -

RESOLVED, that Mr. Richard Barth, Dr. Jean Carvais, Dr. Vincent T. DeVita, Jr., Mr. Robert F. Goldhammer, Mr. David M. Kies, Mr. Paul B. Kopperl, Dr. John Mendelsohn, Mr. William R. Miller, Dr. Samuel D. Waksal and Dr. Harlan W. Waksal, are hereby nominated as the slate of directors to be presented to the stockholders at the 1998 Annual Meeting for their vote thereon; and it is further

Amendments to 1996 ISO Plan and 1996 Non-Qualified Plan-

RESOLVED, that, subject to shareholder approval at the 1998 Annual Meeting, the 1996 Incentive Stock Option Plan (the "1996 ISO Plan") is hereby further amended to increase the total number of shares of the Company's Common Stock which may be issued pursuant to options which may be granted under the 1996 ISO Plan from 3,000,000 to 4,000,000, which number shall be reduced by the number of shares of Common Stock which have been or may be issued pursuant to options granted under the Company's 1996 Non-Qualified Plan Stock Option Plan (the "1996 Non-Qualified Plan"); and it is further

RESOLVED, that the foregoing amendments to the 1996 ISO Plan be presented to the stockholders at the Annual Meeting for their vote thereon; and it is further

RESOLVED, that subject to shareholder approval at the Annual Meeting, the 1996 Non-Qualified Plan is hereby amended to (i) increase the total number of shares of the Company's common stock which may be issued pursuant to options which may be granted under the 1996 Non-Qualified Plan from 3,000,000 to 4,000,000, which number shall be reduced by the number of shares of Common Stock which have been or which may be issued and sold pursuant to options granted under the 1996 ISO Plan; and (ii) increase from 2,500 to 15,000 the annual non-discretionary option grant made to non-employee members of the Board of Directors (other than the Chairman); and (iii) increase from 2,500 to 30,000 the annual non-discretionary option grant made to a non-employee Chairman of the Board of Directors; and it is further

RESOLVED, that the foregoing amendments to the 1996 Non-Qualified Plan be presented to the stockholders at the Annual Meeting for their vote thereon; and it is further

Option Grant to each of Samuel D. Waksal and Harlan W. Waksal -

RESOLVED, that the option grants made at this March 29, 1999 Board Meeting, subject to shareholder approval and the receipt of a favorable opinion from F.W. Cook and Company, to each of Samuel D. Waksal and Harlan W. Waksal to purchase 1,000,000 shares of Common Stock and 650,000 shares of Common Stock, respectively, on the terms set forth herein be submitted to the stockholders at the Annual Meeting for their vote thereon; and it is further

Amendment to Certificate of Incorporation –

RESOLVED, that the amendment to the Company's certificate of incorporation set forth below is hereby declared advisable and is hereby adopted, subject to stockholder approval:

"FOURTH: The total number of shares of capital stock which the Corporation shall have the authority to issue is sixty million (60,000,000) shares of common stock with a par value of one tenth of one cent ($.001) per share and four million (4,000,000) shares of preferred stock with a par value of one ($1.00) per share."

and it is further

RESOLVED, that such amendment be submitted to the stockholders at the Annual Meeting for their vote thereon; and it is further

Selection of Auditors -

RESOLVED, that KPMG LLP is hereby selected to audit the Company's financial statements for the fiscal year ending December 31, 1999; and it is further

Filing and Mailing of Proxy Materials -

RESOLVED, that the proxy statement to be utilized in connection with the Annual Meeting in substantially the form that shall be hereafter submitted to the Board (the "Proxy Statement") is hereby approved; and it is further

RESOLVED, that the officers of the Company are hereby authorized and directed to file with the Securities and Exchange Commission and The Nasdaq Stock Market preliminary and definitive copies of the Proxy Statement, preliminary and definitive copies of the proxy card setting forth the proposals contained in the

Proxy Statement and an Annual Report to Stockholders, consisting of the Annual Report on Form 10-K for the fiscal year ended December 31, 1998 and a letter from the President and CEO and Chairman (which annual report shall be so filed for informational purposes only) (the definitive copies of which are referred to herein collectively as the "Definitive Proxy Material"); and it is further

RESOLVED, that the officers of the Company are hereby authorized and directed, on or about April 26, 1999, to mail to the Company's holders of common stock on April 7, 1999, the record date, the Definitive Proxy Material.

The Board also discussed the status of the Company's efforts in connection with the Y2K compliance issues. This discussion continued that which the officers had with the Board in the past Board meetings. In particular the efforts taking place to ensure Y2K compliance were discussed, as supervised by responsible persons within the Company in each functional area. Functional areas are computer hardware and software, laboratory equipment, research collaborations, manufacturing, and other vendors. Other vendors include banks, insurance companies, brokers, depositories, and pharmaceutical partners of the Company, among others.

It was reported to the Board that computer software and hardware issues were being addressed on a systematic basis, such that each system and type or piece of hardware or software was being examined for its Y2K status. Those systems that are not Y2K compliant are being replaced or modified to bring them into compliance. Systems are then being tested to ensure compliance. A report of each system is being updated by the responsible person for the area, and this report is made available to the Board. As of the meeting of this date, the report includes three systems that are not Y2K compliant within computer hardware and software, and these are Macola 6.0, which is to be updated in April of this year, and the F9 software system, which receives dates from Macola, and so will be updated with Macola. The PBX Definity G1 telephone system is also non-compliant and is being replaced.

It was reported to the Board that critical laboratory equipment and research collaborations were compliant, and that testing had taken place where necessary. In connection with the systems in place at the Company's manufacturing facility in Branchburg, examination has been divided into functional areas of quality control, quality assurance, clinical serology, manufacturing, facility, and process development. Systems in each which are not yet Y2K compliant have been identified, and steps to modify or to replace those systems to bring them into Y2K compliance have been determined and scheduled. Testing of most systems is ongoing. Continued reports to the Board will be provided.

Finally, vendors other than those that supply computer software and hardware and other than those that fall in the functional category related to manufacturing listed above are being identified for the purpose of seeking assurance of Y2K compliance. These are to include banks, capital managers, insurance companies, and brokers, 401K fund managers and outside pharmaceutical partners. The officers indicated that they would keep the Board informed of efforts to obtain such assurances in the immediate future.

There being no further business to come before the Board, a motion to adjourn the meeting was made, seconded and so voted and the meeting was declared adjourned.

A true and accurate record.

Attest: _____
John B. Landes, Secretary

Attachment A

In evaluating the reasonableness of this grant to Dr. Samuel D. Waksal, the Board considered, among other things, the following:

- The critical importance of Dr. Samuel D. Waksal to the Company's ongoing research and development initiatives.
- The difficulty of replacing this individual.
- The objective of providing strong incentive to Dr. Samuel D. Waksal consistent with enhancing shareholder value.
- The vesting requirements placed on this grant.
- The multi-year nature of the award, which essentially serves as an acceleration of grants that might otherwise be made in the future, it being the intent of the Board that there be no additional option grants to Dr. Samuel D. Waksal until 2003 at the earliest.
- The reasonable size of the award compared to the Company's total shares outstanding, both on a primary and fully-diluted basis.

Description of Option

The option will not be granted to Dr. Samuel D. Waksal unless and until shareholder approval is obtained at the annual meeting of shareholders on May 24, 1999. The exercise price will be the last reported sale price of the common stock on May 24, 1999. The option will vest in its entirety on May 24, 2006, except that the option may vest earlier as follows:

Number of Shares	Vesting Date	Target Price of Stock
200,000	May 24, 2000	If for any ten consecutive trading days from May 24, 1999 through May 23, 2000 the last reported sale price of the common stock exceeds $25.
200,000	May 24, 2001	If for any ten consecutive trading days from May 24, 2000 through May 23, 2001 the last reported sale price of the common stock exceeds $34.
200,000	May 24, 2002	If for any ten consecutive trading days from May 24, 2001 through May 23, 2002 the last reported sale price of the common stock exceeds $47.
200,000	May 24, 2003	If for any ten consecutive trading days from May 24, 2002 through May 23, 2003 the last reported sale price of the common stock exceeds $62.
200,000	May 24, 2004	If for any ten consecutive trading days from May 24, 2003 through May 23, 2004 the last reported sale price of the common stock exceeds $75.
1,000,000		

Additionally, the option will vest on any given vesting date for which the applicable target price was achieved as to any shares as to which the option did not vest on any prior vesting date as a result of the target price not having been achieved. For example, assume there are no ten consecutive trading days during the period May 24, 1999 through May 23, 2000 that the last reported sale price of the common stock exceeds $25, and that during the period May 24, 2000 through May 23, 2001 there is a ten consecutive trading day period during which the last reported sale price of the common stock exceeds $34. Under this scenario, Dr. Samuel D. Waksal's option vests as to no shares on May 24, 2000 and as to 400,000 shares on May 24, 2001.

The vesting of the option will accelerate in the event of an acquisition of the Company where Dr. Samuel D. Waksal's position with the Company is terminated.

Once vested as to any shares, the option may be exercised in whole or in part as to such shares from time to time until May 24, 2009 so long as Dr. Samuel D. Waksal remains employed by the Company. Payment of the exercise price of the option must be made in full in cash at the time of exercise. The option will provide for certain adjustments in the event of certain mergers, consolidations, reorganizations, recapitalizations, stock dividends, split-ups continuations or similar events involving the Company or common stock.

The option will otherwise contain usual and customary terms which shall be substantially the same as those contained in the Company's 1996 Non-Qualified Stock Option Plan.

It is the intent of the Board that this grant provides significant retention value and incentive with respect to the continued employment of Dr. Samuel D. Waksal over the next four years, and that there be no additional option grants to him until 2003 at the earliest.

Attachment B

In evaluating the reasonableness of this grant to Dr. Harlan W. Waksal, the Board considered, among other things, the following:

- The critical importance of Dr. Harlan W. Waksal to the Company's ongoing research and development initiatives.
- The difficulty of replacing this individual.
- The objective of providing strong incentive to Dr. Harlan W. Waksal consistent with enhancing shareholder value.
- The vesting requirements placed on this grant.
- The multi-year nature of the award, which essentially serves as an acceleration of grants that might otherwise be made in the future, it being the intent of the Board that there be no additional option grants to Dr. Harlan W. Waksal until 2003 at the earliest.
- The reasonable size of the award compared to the Company's total shares outstanding, both on a primary and fully-diluted basis.

Description of Option

The option will not be granted to Dr. Harlan W. Waksal unless and until shareholder approval is obtained at the annual meeting of shareholders on May 24, 1999. The exercise price will be the last reported sale price of the common stock on May 24, 1999. The option will vest in its entirety on May 24, 2006; except that the option may vest earlier as follows:

Number of Shares	Vesting Date	Target Price of Stock
130,000	May 24, 2000	If for any ten consecutive trading days from May 24, 1999 through May 23, 2000 the last reported sale price of the common stock exceeds $25.
130,000	May 24, 2001	If for any ten consecutive trading days from May 24, 2000 through May 23, 2001 the last reported sale price of the common stock exceeds $34.
130,000	May 24, 2002	If for any ten consecutive trading days from May 24, 2001 through May 23, 2002 the last reported sale price of the common stock exceeds $47.
130,000	May 24, 2003	If for any ten consecutive trading days from May 24, 2002 through May 23, 2003 the last reported sale price of the common stock exceeds $62.
130,000	May 24, 2004	If for any ten consecutive trading days from May 24, 2003 through May 23, 2004 the last reported sale price of the common stock exceeds $75.
650,000		

Additionally, the option will vest on any given vesting date for which the applicable target price was achieved as to any shares as to which the option did not vest on any prior vesting date as a result of the target price not having been achieved. For example, assume there are no ten consecutive trading days during the period May 24, 1999 through May 23, 2000 that the last reported sale price of the common stock exceeds

$25, and that during the period May 24, 2000 through May 23, 2001 there is a ten consecutive trading day period during which the last reported sale price of the common stock exceeds $34. Under this scenario, Dr. Harlan W. Waksal's option vests as to no shares on May 24, 2000 and as to 260,000 shares on May 24, 2001.

The vesting of the option will accelerate in the event of an acquisition of the Company where Dr. Harlan W. Waksal's position with the Company is terminated.

Once vested as to any shares, the option may be exercised in whole or in part as to such shares from time to time until May 24, 2009 so long as Dr. Harlan W. Waksal remains employed by the Company. Payment of the exercise price of the option must be made in full in cash at the time of exercise. The option will provide for certain adjustments in the event of certain mergers, consolidations, reorganizations, recapitalizations, stock dividends, split-ups continuations or similar events involving the Company or common stock.

The option will otherwise contain usual and customary terms which shall be substantially the same as those contained in the Company's 1996 Non-Qualified Stock Option Plan.

It is the intent of the Board that this grant provides significant retention value and incentive with respect to the continued employment of Dr. Harlan W. Waksal over the next four years, and that there be no additional option grants to him until 2003 at the earliest.

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RICHARD BARTH
823 EUCLID
HOUSTON, TEXAS 77009

April 2, 2002

Dear Mr. Goldsmith,

Re: my letter to you of Wed. 3d. 2002,

I confirm that my resignation from the Lucelon Board is effective today.

Yours truly,

Richard Barth

THE 2002 FORTUNE 500

The Socialite Scientist

Bristol-Myers was thrilled to make a deal with Imclone, a hot biotech. But Sam Waksal was more than Bristol bargained for.

FORTUNE
Monday, April 15, 2002
By Andrew Serwer

The brief history of the biotech business is rife with amazing stories, outrageous hubris, booms, and busts. But nothing has come close to the saga of Imclone Systems. Here you have a company that has spawned not just shareholder lawsuits and inquiries from the SEC and the Justice Department but also a full-fledged investigation by a congressional committee. A company that is covered almost daily not just by the Wall Street Journal but also by New York's snarky tabloids. A company run by a guy who's said to be a brilliant scientist but who also pals around with the likes of Mick Jagger and Martha Stewart, and leaves a trail of litigation and bad debts wherever he goes. A company that created the biggest single-product partnership ever between a biotech and an old-line pharma giant--that being Bristol-Myers Squibb (No. 96 on the FORTUNE 500)--which led to the biggest dustup this sector has seen. And all of this before a single dose of Imclone's cancer-fighting drug Erbitux has been sold, never mind approved by the FDA.

At the center of the fiasco is Imclone's CEO, Sam Waksal. Did Waksal compromise or rush studies of Erbitux to push the drug through the FDA? Did he mislead Bristol and Imclone's shareholders last fall when he knew the FDA had issues with Erbitux's application? And did Waksal and his family engage in insider trading of Imclone stock, buying and selling shares before important material events that sent the stock first soaring and then plummeting? Waksal declined to be interviewed for this story. Yet it's hard to believe that in every instance he has been either falsely accused or misunderstood.

The simplest thing to say about Sam Waksal is that he's complicated. There is no doubt that he is a legitimate scientist. "I would say he has far more scientific knowledge and depth of understanding than the majority of CEOs in biotech," says his friend Richard Mulligan, a professor of genetics at Harvard Medical School and a member of Imclone's scientific advisory board. Waksal is also something of a public intellectual--he hosts salons and serves as chairman of the New York Council of the Humanities. But he is also a social climber of the first stripe, with the trappings of a certain kind of Manhattan chic--the glam SoHo apartment, the property in the Hamptons--that keep him in need of cash. Which, of course, puts those questions about Waksal in another light. To put it bluntly: Could it be that Waksal has bent and stretched the truth because he needs the money?

"I wanted to find out about him," says an investor, "so I called up Kroll [the private detective agency] to ask how much it would cost to get a report. The Kroll guy told me, 'Oh, not that much.' I asked him why and he told me, 'Because I've already done about dozen of them for other people.' " The Kroll report lays out a long

history of litigation, missed debt payments, and "questionable dealings."

You might not think that a biotech entrepreneur with that kind of background would be an attractive partner for a $22-billion-a-year stock market stalwart like Bristol-Myers Squibb. And yet, by last year, Bristol was urgently in need of drugs to fill its pipeline. Its cancer drug Taxol, made with the bark of the yew tree, had lost most of its patent protection. Bristol had tried and failed to form a partnership with another biotech company, OSI, that has a promising cancer drug.

The story of Imclone and Bristol would be just one more corporate soap opera were it not for one thing. Thousands of cancer patients are right now waiting for Erbitux to be approved. Every lawsuit filed against Imclone, every meeting with congressional investigators, delays that process. And when you talk to folks in the world of cancer research, they will tell you that Erbitux holds great promise. At least in combination with another drug, it appears to neutralize tumors in colorectal-cancer patients. And unlike chemotherapy, it does not seem to have dire side effects. "You can be as negative as you want about Waksal, the company, and how they've developed the drug, but the fact is this is a drug with signs of clinical activity," says Dr. Lance Willsey, who helps run DCF Capital, a health-care hedge fund.

Some try their best to ignore Waksal. "I focus on two points," says T. Rowe Price fund manager Kris Jenner, who has owned Imclone for years. "Is Erbitux a drug that works? And will this drug get approval at some point? The answers to both questions are yes. As for the other stuff, I try to block it out." Ah, Kris, if it were only that simple.

Samuel D. Waksal was born in 1949, according to his curriculum vitae, or in 1947, according to the company proxy (his spokesman says he assumes the birthdate on the c.v. is a typo). He grew up in Dayton. Both his parents are listed as Holocaust survivors by the U.S. Holocaust Memorial Museum. He received a Ph.D. in immunology from Ohio State in 1974, with a dissertation entitled "In Vitro Studies on Thymus Derived Lymphocytes: Differentiation of T-Lymphocytes and Their Function in Tumor Destruction." For years Waksal and his younger brother Harlan, who is an M.D., worked at medical research jobs at prestigious institutions such as the National Cancer Institute, Stanford University Medical Center, Tufts University Research Center, and Mount Sinai School of Medicine.

Throughout his career, though, Sam Waksal has been dogged by charges that he is difficult to get along with. Waksal acknowledges that he made enemies at Mount Sinai. Harlan, whom acquaintances describe as the more grounded of the two brothers--he is now a family man in New Jersey--was arrested in 1981 at the Fort Lauderdale airport with two pounds of cocaine wrapped in underpants in his carryon bag. The charges were dropped on a technicality.

Sam and Harlan Waksal founded Imclone in 1984 (Harlan is the COO), hoping to find commercial applications for the work they were doing. But they didn't have much luck until they met the esteemed cancer researcher Dr. John Mendelsohn. Now president of the MD Anderson Cancer Center in Houston and a member of Imclone's board (also of Enron's), Mendelsohn was working on a promising cancer-fighting molecule, a monoclonal antibody called 225. A hybrid of human and mouse antibodies, 225 works to inhibit the growth of tumor cells. Mendelsohn had helped develop the molecule at the University of California at San Diego in the early 1980s; 225 was licensed from the University of California to a company later bought by Eli Lilly. But Lilly dropped the license because it was concerned about the possible toxicity of certain monoclonal antibodies, Mendelsohn says.

And so the license reverted to the University of California, with Mendelsohn out

there essentially looking to broker it. "In 1993, I met the Waksals through a mutual friend," Mendelsohn says. "They were looking for something they could license and get a jump-start on. So they contacted the University of California and negotiated a license."

Biotech ventures often take a decade or more before they are able to sell a product. Research, testing, and FDA approval are all complex endeavors. As Imclone began this protracted journey, questions about Waksal and his company were already being raised. The same year Imclone licensed 225, an article in Barron's reported that Waksal was investing in restaurants with Mariel Hemingway and her husband, and with Martha Stewart's daughter Alexis. The story also reported that Imclone had made a series of loans and advances to Waksal, some of which bore no interest.

According to the Kroll report, Sam Waksal seems to have developed a pattern of forming partnerships for real estate, restaurant, and small business ventures and then borrowing money from these ventures and not paying it back. Over the past 20 years, the report shows, dozens of lawsuits and tax liens have been filed against Waksal by the IRS, New York State, American Express, banks and brokers, art galleries, contractors, and individuals. Most claims were eventually settled or paid. A recent example was a lawsuit filed by a New York executive named Tina Sharkey, whom Waksal hired to run Ibeauty.com, an Internet company Waksal helped found (Martha Stewart was on the board). Sharkey alleged that Waksal "stiffed" her out of nearly $380,000 in compensation. Sharkey charged that Waksal had told her that Ibeauty had between $10 million and $15 million in cash, that it was on track to triple its revenues, and that a top Internet analyst from Morgan Stanley was interested in taking the company public. All that was untrue, Sharkey says. The suit was settled. Waksal declined to comment on the case.

In the late 1980s, besides working on making 225 (now called Erbitux) into a drug, Waksal was busy climbing New York's social ladder. He bought a swanky loft in SoHo in 1989, and then added on to it. What's it look like? Well, if you were to shoot a movie and wanted a "SoHo loft" location, Waksal's might very well be it. Some 5,000 square feet, the apartment is immaculately and eclectically appointed, and it's continually being renovated; recently workers were busy replacing the living room's round columns with square ones. Paintings by Rothko, Bacon, de Kooning, Picasso, and Twombly grace the walls. One estimate places the art collection's value in excess of $20 million. The Kroll report shows that in 1999, 21 pieces from the collection were put up as collateral for a loan from NationsBank (now Bank of America).

Waksal's parties--or salons--are known for drawing celebrities and beautiful women. Mick Jagger showed up at his Christmas bash. (A picture of Jagger and Waksal in New York magazine hangs in the offices of at least two short-sellers of Imclone stock.) At an event on March 7 of this year sponsored by the New York Council of the Humanities, paleontologist Stephen Jay Gould spoke. Says a TV personality who attended one of Waksal's soirees a while back: "The whole thing was a little over the top. Too much decolletage for me. I grabbed my husband and got him out of there."

As fast and furious as Waksal's social life was, though, Imclone appeared to be bogged down. The Waksals took their company public in late 1991, but monoclonal antibodies had fallen out of favor--proving harder to produce and more expensive than conventional small-molecule drugs--and by early 1995 the company's stock had dropped to a low of 19 cents a share (split adjusted). At that juncture, Waksal's socializing may have saved his business. He had befriended billionaire Carl Icahn over tennis in the Hamptons. Word on the street is that Waksal begged Icahn to invest a couple of million, which Icahn did.

Over the next several years studies began to show that Erbitux was an effective cancer fighter. In 1998, Imclone sold the European rights to Germany's Merck KGaA (which has been separate from U.S. Merck since 1917) for about $60 million. In May 2000 a trial study demonstrated that a woman's deadly cancer went into remission apparently because of Erbitux.

If Erbitux was going to be a hit, the Waksals knew they would need a major drug company as a partner. Small companies can develop biotech drugs effectively, but marketing them requires a sales force. Imclone eyed all the big players, but it gravitated to Bristol-Myers Squibb.

The two companies were dissimilar yet complementary. New-age Imclone is headquartered in a former shoe factory in Manhattan's trendy TriBeCa. Old-school Bristol has its headquarters on Park Avenue and is run by Peter Dolan, a young, squarish, non-Waksal type. Bristol's board includes IBM's Lou Gerstner and former American Express CEO Jim Robinson. Though Bristol is best known for over-the-counter products like Excedrin and Bufferin, those in the pharma business often call it "the cancer company" for its drug Taxol and other cancer-fighting therapies.

For all its size and marketing prowess, though, Bristol has some serious issues. The stock recently traded at a five-year low after tests failed to show that a Bristol heart drug was better than a cheap generic. Bristol has even been mentioned as a potential takeover target lately, with Novartis as a possible buyer.

Imclone, with its tantalizing cancer drug, had ties to the big drug company; former Bristol vice chairman William Miller has served on Imclone's board since 1996, and the biotech company's CFO, Dan Lynch, is a former Bristol executive. So while at least seven other drug companies looked at Erbitux and Imclone, Bristol was the natural fit.

By 2000 Imclone was meeting with the FDA to determine whether a 120-patient study it had started would be sufficient to gain fast-track approval, a procedure that allows a company to seek clearance for a potentially life-extending drug based on small trials, instead of more traditional large ones. A sticking point was the design of the trial, which tracked patients using Erbitux who didn't respond to another therapy, in this case a chemotherapy drug called irinotecan. Patients were given Erbitux and irinotecan together, and some showed signs of improvement. The FDA was apparently sanguine about Erbitux but concerned that the trial didn't clarify its efficacy as a single agent. Still, in February of last year, the FDA granted Erbitux fast-track status.

By then, Imclone was no longer a penny-ante stock. IMCL was soaring--hitting a peak of $84 in March 2000--as positive buzz about Erbitux circulated on Wall Street. Some of the buzz came from Waksal himself; he told Bloomberg, for instance, that Erbitux "is going to be the most important new oncology launch ever."

At a May meeting of the American Society of Clinical Oncology, Dr. Leonard Saltz, an eminent Memorial Sloan-Kettering Cancer Center oncologist who was the principal investigator of the Imclone study, reported that Erbitux helped 22.5% of the people in the 120patient trial. "Knock-your-socks-off exciting" is how Saltz described the findings. Imclone celebrated as only Waksal knew how, staging a Doobie Brothers concert for the assembled oncologists.

Imclone was now negotiating with Bristol in earnest. According to people present at the meetings, the man in charge on the Bristol end was Peter Dolan, who had

come up through the marketing side of the company. Last May the two sides agreed to a deal in which Bristol would buy a controlling interest in Imclone, between 51% and 60%, at $65 a share, to be paid for in a tax-free exchange of Bristol stock. But when Dolan took this deal to his board, says a source privy to the talks, the directors--particularly Gerstner and Robinson--balked. They told Dolan he should cut down the size of the deal.

Last summer, while the negotiations with Bristol were hot and heavy, Imclone loaned the Waksal brothers some $35 million to exercise stock options. The Waksals bought some 2.8 million shares priced at between $3 and $9 a share when the stock was selling for $40. They didn't sell their shares, though, betting instead that the stock would go higher.

It was a good bet. On Sept. 19, Bristol agreed to a scaled-down deal with Imclone. Bristol would pay about $1 billion for a 20% stake at $70 a share (the stock had appreciated since May), a 40% premium over its current price. Bristol would also lay out $200 million at that point, and another $800 million as Erbitux reached critical milestones, and it would market the drug, reportedly in return for 40% of profits. That $2 billion marked the biggest single-product deal ever made in biotech.

How would this play out for Bristol? Well, if Erbitux turned out to be a $1-billion-a-year drug, Bristol could reap as much as $400 million annually. The $1 billion equity investment would provide an equity kicker if the drug was successful and Imclone's stock climbed. But the deal was risky, and if Bristol were to profit, everything would have to work out perfectly. Needless to say, things didn't.

What happened after Bristol bought its Imclone stake has been the subject of endless speculation and hundreds of news articles. We know that on Oct. 30, Bristol tendered for its Imclone stake, and that the Waksals reaped a $111 million windfall on the options they exercised over the summer. We also know that Imclone submitted a formal application for approval of its trial to the FDA on Oct. 31. We also know that Harlan Waksal sold another 700,000 shares at $71, garnering another $49 million plus. The other thing we know is that all hell broke loose.

The trouble came slowly at first: An obscure research firm, Sterling Financial, warned as early as October that Imclone's trial might not be a slam-dunk. In December, rumors that something was amiss with the FDA picked up steam. Imclone's stock began slipping a couple of points a day. In a remarkably prescient move, Waksal's daughter Aliza sold $2.5 million worth of Imclone stock on Dec. 27. The very next day, Friday, Dec. 28, at 7:14 p.m., the suspense was broken. Imclone put a press release out over the wire. The FDA had refused to accept the Erbitux application.

Wall Street's reaction was brutal. The stock plunged from $55 to $46 on huge volume as analysts scurried to downgrade it. And yet initially Sam Waksal said the FDA's "refuse to file" letter was no big deal. He told Reuters that the FDA simply wanted more "annotation and measurement" information about how the company conducted its trial. For a day or two, Imclone's stock stabilized in the 40s. Then came another bombshell. On Jan. 4, the Cancer Letter, a Washington, D.C., scientific newsletter, got hold of the FDA letter and reported that the problems went far beyond annotation and measurement. Calling the application "scientifically incomplete," the nine-page letter--which Fortune has also obtained--details serious concerns by the FDA. The next trading day, Jan. 7, Imclone stock crashed again on huge volume. The first shareholder lawsuit was filed.

It is possible that the FDA is not blameless in this imbroglio. The agency has had no head for more than a year, and critics say the guidance it offers is increasingly inconsistent and unclear. On the other hand, Imclone had little experience dealing

with the FDA, and the company might well have misread its communication. Waksal himself said recently: "We screwed up."

January 2002 was a terrible month for Sam Waksal and Imclone. When Waksal finally acknowledged that the FDA had expressed concerns about the Erbitux trial throughout the fall, more shareholder lawsuits flooded in. Now if Waksal was sugarcoating bad news for shareholders, he just might have picked the single worst time in history to do so--smack-dab in the middle of the Enron outcry. On Jan. 18, trading in Imclone stock was halted after the House Energy and Commerce Committee (the same committee investigating Enron) announced that it was beginning an inquiry into Imclone. On Jan. 24, the SEC said it was investigating. On Jan. 25, the Justice Department piled on.

Bristol's executives were steaming mad. After all, by the end of January, Bristol's holdings of Imclone's stock had plunged from $1 billion to $215 million, and the company was taking a beating in the press. How could Bristol be so completely duped? One source close to the negotiations says that Peter Dolan faced harsh questions from the board, particularly from Gerstner, over the deal. That may explain the next strange turn of events.

On Feb. 5, Bristol officials issued a press release, showing it to Imclone only at the last minute. As one informed banker put it, the release was "a corporate temper tantrum." Dolan was demanding the removal of the Waksal brothers; he wanted complete control of Erbitux; and he wanted to rewrite the licensing deal. If Imclone didn't agree to these demands, Bristol might walk. "We were shocked," says a person in the Imclone camp. "We knew that we should sit down and talk, but why the public ultimatum?" The answer, some speculate, could be that Dolan was blasting Imclone publicly for the benefit of Bristol's board. In any event, days later Imclone's board rejected Bristol's demands.

As if that weren't enough, Carl Icahn entered the fray. He had, no doubt to his own amazement, made more than $100 million on his investment of about $2 million in Imclone back in 1995. On Feb. 15, Icahn filed papers with the Federal Trade Commission and the Department of Justice seeking to buy up to $500 million of Imclone's stock. The stock price had dropped so low it looked cheap to him. Icahn could buy half the company for $500 million, when Bristol had just paid $1 billion for 20%.

Imclone immediately filed a so-called poison-pill plan, which is triggered in the event of a hostile takeover. That seemed strange because Icahn and Waksal were friends. Icahn was apparently told that Imclone had to prevent a takeover because a change in control of Imclone would deep-six its contract with Bristol-Myers. Still, the prospect of an Icahn takeover drove up Imclone's stock price temporarily, even as the Cancer Letter published a report in which a group of scientists concluded that the company would not receive a favorable review at its FDA meeting scheduled for late February. (In yet another remarkable twist, the same issue of the Cancer Letter reported that Arnold Levine, an Imclone board member, was resigning as president of Rockefeller University after he was reportedly caught in a campus lounge smooching with a female research assistant.)

Meanwhile, short-sellers, who made millions on Imclone's stock in January, were still betting heavily against the stock in February, waiting for the outcome of Imclone's Feb. 26 meeting with the FDA. "I really thought the FDA was going to tell Imclone to go back to the drawing board," said a hedge-fund manager. But of course, the unexpected happened. The FDA said it might not require a full-scale independent trial. Instead it would look at data gathered by Imclone's European partner, Merck KGaA. The market took that as good news, or at least not more

bad news. By late March the stock had rebounded from $15 to $26.

Almost immediately, Imclone and Bristol began to rework their relationship. Bristol of course wanted to pay less, and Imclone was willing to give on that point because the Erbitux rollout was to be delayed. The two sides worked over the weekend and nailed down the agreement on March 5 at Imclone's offices on Varick Street.

Basically Bristol will pay Imclone $100 million less than before. It will shell out $140 million now and another $60 million a year later. Bristol will pay an additional $500 million in two payments, for a total of $700 million, vs. the originally agreed upon $800 million. "The new agreement is important in a few ways," says T. Rowe Price's Jenner. "It preserves the relationship between two companies that need each other, and it also suggests that Bristol does not believe that it was defrauded by Imclone."

So what's next? Well, almost everyone agrees that it is still a long, bumpy road for Erbitux. Icahn, it is said, has become concerned because he isn't so sure the FDA will move ahead quickly on the drug. The delay in approving Erbitux has conferred advantages on some competing drugs, namely AstraZeneca's Iressa--which could be approved this year--and OSI's Tarceva.

Imclone still faces the government investigations and lawsuits. The House committee recently requested all records relating to Sam Waksal's accounts and those of family members. Under the circumstances, can Waksal keep this ship on course? "With the heavy hand of Bristol on his shoulder, he just might do it," says one hedge-fund manager.

Of course, what turns this whole drawn-out farce into tragedy is that there is a group of true losers here. Not the shorts or the longs, nor Bristol, nor the Waksals, but the colorectal-cancer patients who might be benefiting from Erbitux if the drug had been approved by now. Sadly, what keeps getting lost time and time again in the Imclone saga is the importance of this work. After all, they're trying to cure cancer here.

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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

SCHEDULE 14A

Proxy Statement Pursuant to Section 14(a) of the Securities
Exchange Act of 1934 (Amendment No.)

Filed by the Registrant [X]

Filed by a Party other than the Registrant [ ]

Check the appropriate box:

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[ ] Preliminary Proxy Statement
[ ] Confidential, for Use of the Commission Only (as permitted by Rule 14a-6(e)(2))
[X] Definitive Proxy Statement
[ ] Definitive Additional Materials
[ ] Soliciting Material Pursuant to Section 240.14a-12
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ImClone Systems Incorporated

(Name of Registrant as Specified In Its Charter)

(Name of Person(s) Filing Proxy Statement, if other than the Registrant)

Payment of Filing Fee (Check the appropriate box):

[X] No fee required

[ ] Fee computed on table below per Exchange Act Rules 14a-6(i)(1) and 0-11.

(1) Title of each class of securities to which transaction applies:

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(3) Per unit price or other underlying value of transaction computed pursuant to Exchange Act Rule 0-11 (set forth the amount on which the filing fee is calculated and state how it was determined):

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(1) Amount Previously Paid:

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(2) Form, Schedule or Registration Statement No.:

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[IMCLONE LOGO]

IMCLONE SYSTEMS INCORPORATED
180 VARICK STREET
NEW YORK, NY 10014
(212) 645-1405

NOTICE OF ANNUAL MEETING OF STOCKHOLDERS

DATE: MAY 23, 2002
TIME: 10:00 A.M. (LOCAL TIME)
PLACE: HOTEL W NEW YORK
541 LEXINGTON AVENUE
(BETWEEN 49TH AND 50TH STREETS)
NEW YORK, NEW YORK 10022

ITEMS OF BUSINESS:

1. Election of eleven directors.

2. Approval of the ImClone Systems Incorporated 2002 Stock Option Plan.

3. Approval of an amendment to the Company's Certificate of Incorporation, as amended, to increase the number of shares of common stock the Company is authorized to issue from 120,000,000 to 200,000,000 shares.

4. Ratification of the appointment of KPMG LLP as the Company's independent certified public accountants for the fiscal year ending December 31, 2002.

5. Any other matters properly brought before the stockholders at the meeting.

RECORD DATE:

Only holders of the common stock of record at the close of business on April 16, 2002 are entitled to notice of and to vote at the meeting or any postponements or adjournments thereof.

ANNUAL REPORT:

Our 2001 Annual Report, which is not a part of the proxy soliciting material, is enclosed.

PROXY VOTING:

It is important that your shares be represented and voted at the meeting. To vote, please complete, sign and date the enclosed proxy and promptly return it in the envelope provided or submit your vote by telephone or via the Internet. Sending in your proxy will not prevent you from voting in person at the meeting.

By Order of the Board of Directors

/s/ Daniel S. Lynch

Daniel S. Lynch
Secretary

New York, New York
April 29, 2002
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IMCLONE SYSTEMS INCORPORATED
180 VARICK STREET
NEW YORK, NEW YORK 10014

PROXY STATEMENT

This proxy statement is furnished in connection with the solicitation of proxies for use at the Annual Meeting of Stockholders of ImClone Systems Incorporated (the "Company") to be held at 10:00 a.m., local time, on Thursday, May 23, 2002, at Hotel W New York, 541 Lexington Avenue (between 49th and 50th Streets), New York, New York 10022, and at any postponements or adjournments thereof. The Notice of Annual Meeting, this proxy statement and the accompanying proxy card are first being mailed to stockholders on or about April 29, 2002.

ABOUT THE MEETING

WHAT IS THE PURPOSE OF THE MEETING?

At the meeting, stockholders will act upon the matters outlined in the accompanying notice of meeting, including the election of Directors, approval of the ImClone Systems Incorporated 2002 Stock Option Plan, approval of an amendment to the Company's Certificate of Incorporation, as amended, to increase the number of authorized shares of common stock and ratification of the appointment of the Company's independent auditors. In addition, the Company's management will report on the performance of the Company during fiscal 2001.

WHO MAY ATTEND THE MEETING?

Although we encourage you to complete and return the proxy card or to vote by telephone or via the Internet to ensure that your vote is counted, you may attend the meeting and vote your shares in person. All stockholders as of the record date, or their duly appointed proxies, may attend the meeting. If you hold your shares in "street name" (that is, through a broker or other nominee), you will need to bring a copy of a brokerage statement reflecting your stock ownership as of the record date. In all cases, you must bring a form of personal identification. To ensure the availability of adequate space for the Company's stockholders wishing to attend the meeting, priority seating will be given to stockholders of record, stockholders who hold their shares in street name and invited guests of management. In addition, each stockholder may bring one guest.

In order that seating may be equitably allocated, a stockholder wishing to bring more than one guest must write to the Secretary of the Company in advance of the meeting and receive written concurrence.

WHO IS ENTITLED TO VOTE?

Only stockholders of record at the close of business on the record date, April 16, 2002, are entitled to receive notice of the meeting and to vote the shares of common stock that they held on that date at the meeting or any postponements or adjournments thereof. Each outstanding share entitles its holder to cast one vote on each matter to be voted upon at the meeting.

Pursuant to our Stockholder Agreement with Bristol-Myers Squibb Company ("BMS"), during the period in which BMS has the right to nominate at least one Director to our Board of Directors (a "BMS Director"), BMS and its affiliates are required to vote all of their shares in the same proportion as the votes cast by all of our other stockholders with respect to the election or removal of non-BMS Directors. BMS has the right to nominate at least one BMS Director if its ownership interest in the Company is 5% or greater.

WHAT CONSTITUTES A QUORUM?

The presence at the meeting, in person or by proxy, of the holders of a majority of the shares of common stock outstanding on the record date will constitute a quorum, permitting business to be conducted at the meeting. As of the record date, the Company had 73,343,281 shares of common stock outstanding. Proxies

received but marked as abstentions and broker non-votes will be included in the calculation of the number of shares considered to be present at the meeting.

WHAT VOTE IS REQUIRED TO APPROVE EACH ITEM?

Election of Directors. The affirmative vote of a plurality of the votes cast at the meeting is required for the election of Directors. This means that the individuals who receive the highest number of votes will be elected as Directors, up to the maximum number of Directors to be chosen at the meeting.

Amendment of Certificate of Incorporation. The affirmative vote of the holders of a majority of the shares outstanding on the record date will be required for approval.

Other Items. For each other item, the affirmative vote of the holders of a majority of the shares present in person or represented by proxy and entitled to vote on the item will be required for approval.

WHAT ARE THE RECOMMENDATIONS OF THE BOARD OF DIRECTORS?

The persons named as proxy holders on the proxy card will vote in accordance with the recommendations of the Board of Directors (the "Board"). The Board's recommendation is "FOR" each of the items set forth in this proxy statement. With respect to any other matter that properly comes before the meeting, the proxy holders will vote as recommended by the Board or, if no recommendation is given, in their own discretion.

HOW DO I VOTE?

You may vote in the following ways:

(a) In person: You may vote in person at the meeting. If you hold your shares in street name, you must obtain a legal proxy, executed in your favor, from your broker or nominee if you wish to vote your shares at the meeting.

(b) In writing: If you complete and properly sign the accompanying proxy card and return it to the Company, it will be voted as you direct. If you sign and return your proxy card but do not give voting instructions, the proxy holders will vote your shares as recommended by the Board of Directors. If you are a record holder and attend the meeting, you may deliver your completed proxy card in person. If you hold your shares in street name, your broker or nominee has enclosed or provided a voting instruction form for you to use in directing the broker or nominee how to vote your shares.

(c) By telephone: Call the toll-free telephone number on your proxy card to vote by telephone. You must have a touch-tone telephone to use this option. You will need to follow the instructions on your proxy card and the voice prompts.

(d) Via the Internet: Go to the website listed on your proxy card to vote via the Internet. You will need to follow the instructions on your proxy card and on the website.

Telephone and Internet voting options are available 24 hours a day, seven days a week. When prompted, you will need to enter the control number shown on your proxy card. You will then be able to vote your shares and confirm that your instructions have been properly recorded. If you vote by telephone or via the Internet, your electronic vote authorizes the named proxies in the same manner as if you signed, dated and returned your proxy card. The telephone and Internet voting procedures, including the use of control numbers found on the proxy cards, are designed to authenticate stockholders' identities, to allow stockholders to vote their shares of common stock and to confirm that their instructions have been properly recorded. If you vote by telephone or via the Internet, you do not need to return your proxy card. If you hold your shares in street name, you may vote by telephone or via the Internet if your broker or nominee makes these methods available, in which case the broker or nominee will enclose the instructions with this proxy statement.

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WHAT IF I AM A BENEFICIAL OWNER RATHER THAN A HOLDER OF RECORD?

If your shares are held in a stock brokerage account or by a bank or other nominee, you are considered to be the beneficial owner of shares held in street name. These proxy materials are being forwarded to you by your broker or nominee, who is considered to be the holder of record with respect to your shares. As the beneficial owner, you have the right to direct your broker or nominee as to how to vote by filling out the voting instruction form provided by your broker or nominee. Telephone and Internet voting options may also be available to beneficial owners. As a beneficial owner, you are also invited to attend the meeting, but you must obtain a legal proxy from the holder of record of your shares in order to vote in person at the meeting.

IF I HOLD MY SHARES IN A BROKERAGE ACCOUNT AND DO NOT RETURN VOTING INSTRUCTIONS, WILL MY SHARES BE VOTED?

If your shares are held in street name, your broker or nominee will ask you how you want your shares to be voted. If you provide voting instructions,

your shares must be voted as you direct. If you do not furnish voting instructions, one of two things can happen, depending upon whether a proposal is "routine." Under the rules that govern brokers who have record ownership of shares beneficially owned by their clients, brokers have discretion to cast votes on routine matters, such as the election of directors and ratification of the appointment of independent auditors, without voting instructions from their clients. Brokers are not permitted, however, to cast votes on "non-routine" matters without such voting instructions. A "broker non-vote" occurs when a broker holding shares for a beneficial owner does not vote on a particular proposal because the broker does not have discretionary voting power for that proposal and has not received voting instructions from the beneficial owner. The Company believes that all of the proposals being submitted for stockholder approval at the meeting are routine and, accordingly, does not expect there to be any broker non-votes at the meeting.

CAN I CHANGE MY VOTE AFTER I RETURN MY PROXY?

Yes. Even after you have submitted your proxy, you may change your vote at any time before the proxy is exercised by filing a notice of revocation or an executed proxy card bearing a later date with the Secretary of the Company at the Company's principal executive offices at 180 Varick Street, New York, New York 10014. You may also change or revoke your proxy by telephone or via the Internet at any time before the meeting in accordance with the instructions on the enclosed proxy card. The powers of the proxy holders will be suspended if you attend the meeting in person and so request, although attendance at the meeting will not by itself revoke a previously granted proxy.

HOW ARE VOTES COUNTED?

For purposes of determining the presence of a quorum, abstentions and broker non-votes will be counted by the Company as present at the meeting. Abstentions and broker non-votes will not be voted either in favor of or against any of the proposals. For the election of directors, which requires a plurality of the votes cast, votes withheld from one or more nominees will be excluded entirely from the vote and will have no effect on the outcome. For the proposed Amendment to the Company's Certificate of Incorporation, which requires the affirmative vote of the holders of a majority of the shares outstanding on the record date, abstentions will not be counted and will have no effect on the outcome. For each of the other proposals, which will be decided by the affirmative vote of the holders of a majority of the shares present in person or represented by proxy and entitled to vote on such proposal, abstentions will be counted for purposes of determining the number of votes cast on the proposal and will have the same effect as negative votes.

WHO PAYS FOR THIS PROXY SOLICITATION?

We do. In addition to sending you these materials, some of our employees may contact you by telephone, by mail, or in person. None of these employees will receive any extra compensation for doing this. In addition, we have retained Georgeson Shareholder Communications, Inc. to assist us in soliciting your proxy for a fee of $6,000 plus reasonable out-of-pocket expenses.

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STOCK OWNERSHIP

WHO ARE THE LARGEST OWNERS OF THE COMPANY'S STOCK?

Except as set forth in the table below, the Company knows of no single

person or group of related persons that is the beneficial owner of more than 5% of the Company's common stock. This is based solely on Schedule 13G and Schedule 13D reports filed with the Securities and Exchange Commission (the "SEC") as of March 15, 2002.

HOW MUCH STOCK DO CERTAIN BENEFICIAL OWNERS, THE COMPANY'S DIRECTORS AND EXECUTIVE OFFICERS OWN?

The following table shows the amount of common stock of the Company beneficially owned (unless otherwise indicated) by persons or groups of related persons that beneficially own greater than 5% of the Company's common stock, the Company's current Directors, the Named Executive Officers in the Summary Compensation Table below and the current Directors and executive officers of the Company as a group. Except as otherwise indicated, all information is as of March 15, 2002. "Beneficial Ownership" is a technical term defined by the SEC to mean more than ownership in the usual sense. For example, you "beneficially own" the Company's common stock if you own it directly or indirectly (e.g., through a relationship, a position as a trustee or through an agreement) or if you have the right to acquire it within 60 days (e.g., upon the exercise of options). The table below, as well as all other portions of this proxy statement, reflects the Company's 2-for-1 stock split, effected in the form of a dividend, in October 2000.

<Table>
<Caption>

NAME AND ADDRESS OF BENEFICIAL OWNER(1)	AMOUNT AND NATURE OF BENEFICIAL OWNERSHIP	PERCENT CLASS(2
<S>	<C>	<C>
Bristol-Myers Squibb Company 345 Park Avenue New York, New York 10154	14,392,003(3)	19.63%
FMR Group 82 Devonshire Street Boston, Massachusetts 02109	10,974,541(5)	14.90%
Harlan W. Waksal, M.D.	3,106,847(6)	4.22%
Robert F. Goldhammer	1,461,121(7)	1.99%
Samuel D. Waksal, Ph.D.	581,985(8)	*
David M. Kies	400,008(9)	*
John Mendelsohn, M.D.	373,226(10)	*
Vincent T. DeVita, Jr., M.D.	236,555(11)	*
Peter Bohlen, Ph.D.	212,954(12)	*
Paul B. Kopperl	193,556(13)	*
William R. Miller	158,971(14)	*
Arnold J. Levine, Ph.D.	106,145(15)	*
S. Joseph Tarnowski, Ph.D.	95,061(16)	*
Daniel S. Lynch	15,000(17)	*
Andrew G. Bodnar, M.D.(18)	0	*
Peter S. Ringrose, Ph.D.(18)	0	*
All Directors and Executive Officers as a Group (24 persons)	8,132,776(19)	10.69%

</Table>

* Less than 1%

(1) Unless otherwise noted, each person's address is in care of ImClone Systems Incorporated, 180 Varick Street, Sixth Floor, New York, New York 10014.

(2) The percentage of voting stock owned by each stockholder is calculated by dividing (1) the number of shares deemed to be beneficially held by such stockholder as of March 15, 2002, as determined in accordance with Rule 13d-3 of the Securities Exchange Act of 1934, as amended (the "Exchange

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Act"), by (2) the sum of (A) 73,333,889, which is the number of shares of common stock outstanding as of March 15, 2002, plus (B) the number of shares of common stock issuable upon exercise of currently exercisable options and other derivative securities held by such stockholder. For purposes of this security ownership table, "currently exercisable options" consist of options exercisable as of March 15, 2002 or within 60 days after March 15, 2002. Except as indicated by footnote, the persons named in the table have sole voting and investment power with respect to all shares of common stock shown as beneficially owned by them.

(3) This information is as of March 6, 2002 and was obtained from Amendment No. 2 to Schedule 13D, filed with the SEC on March 6, 2002.

(4) These percentages have been calculated based upon the number of shares reported as beneficially owned in the stockholder's latest Schedule 13G or Schedule 13D filing prior to March 15, 2002 and the number of shares outstanding as of March 15, 2002.

(5) This information is as of December 31, 2001 and was obtained from Amendment No. 2 to Schedule 13G, filed with the SEC on February 14, 2002. This number consists of 10,974,541 shares beneficially owned by Fidelity Management & Research Company, a wholly-owned subsidiary of FMR Corp. and a registered investment adviser, as a result of acting as an investment adviser to various registered investment companies. The shares owned by the investment companies include 50,826 shares of common stock resulting from the assumed conversion of $2,800,000 principal amount of ImClone Systems Incorporated 5 1/2% convertible notes due 3/01/05 (144A) (18.152 shares of common stock for each $1,000 principal amount of debenture) and 251,405 shares of common stock resulting from the assumed conversion of $13,850,000 principal amount of ImClone Systems Incorporated 5 1/2% convertible notes due 3/01/05 (18.152 shares of common stock for each $1,000 principal amount of debenture). FMR Group is the parent company of various Fidelity funds and related parties. Edward C. Johnson 3d, Chairman of FMR Corp., and Abigail P. Johnson, a Director of FMR Corp., are also listed on the Schedule 13G as beneficial owners of the 10,974,541 shares.

(6) Includes 333,334 shares issuable upon the exercise of currently exercisable options; 4,086 shares owned by Dr. Waksal's sons and 157 shares owned in a joint account with his wife.

(7) Includes 120,000 shares issuable upon the exercise of currently exercisable options and 11,785 shares held by Mr. Goldhammer's spouse.

(8) Includes 416,668 shares issuable upon the exercise of currently exercisable options.

(9) Includes 60,000 shares issuable upon the exercise of currently exercisable options; 30,000 shares held by a family foundation of which Mr. Kies is one of the trustees; 16,400 shares held as co-trustee for a trust for Mr. Kies' minor son and 615 shares held by Mr. Kies' spouse as to which Mr. Kies disclaims beneficial ownership.

(10) Consists of 373,226 shares issuable upon the exercise of currently exercisable options.

(11) Includes 236,084 shares issuable upon the exercise of currently exercisable options.

(12) Includes 208,667 shares issuable upon exercise of currently exercisable options.

(13) Consists of 53,570 shares issuable upon the exercise of currently exercisable options; an aggregate of 139,486 shares held by two trusts of which Mr. Kopperl is sole beneficiary and 500 shares held by Mr. Kopperl's spouse as to which Mr. Kopperl disclaims beneficial ownership.

(14) Includes 60,000 shares issuable upon exercise of currently exercisable options.

(15) Includes 76,474 shares issuable upon exercise of currently exercisable options.

(16) Includes 86,176 shares issuable upon exercise of currently exercisable options.

(17) Consists of 15,000 shares issuable upon exercise of currently exercisable options.

(18) Address is in care of Bristol-Myers Squibb Company, 345 Park Avenue, New York, New York 10154.

(19) Includes an aggregate of (1) 2,753,691 shares issuable upon the exercise of currently exercisable options and (2) 1,115 shares as to which beneficial ownership is disclaimed.

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PROPOSAL NO. 1

ELECTION OF BOARD OF DIRECTORS

An entire Board of Directors, consisting of eleven members, will be elected at the meeting. The Directors elected will hold office until their successors are elected, which normally would be expected to occur at the next annual meeting.

Pursuant to a Stockholder Agreement, dated as of September 19, 2001, among the Company, Bristol-Myers Squibb Company and Bristol-Myers Squibb Biologics Company, the size of the Board of Directors was increased from ten to twelve members, and Bristol-Myers Squibb Company received the right to nominate two Directors so long as its ownership interest in the Company is 12.5% or greater.

On April 2, 2002, Richard Barth resigned from the Board of Directors. On April 3, 2002, the Board of Directors fixed the size of the Board at eleven members.

Nominations. At the meeting, the Board of Directors expects to nominate the eleven persons named in this proxy statement as Directors. Although we do not know of any reason why any of these nominees might not be able to serve, the

Board of Directors may propose a substitute nominee if any nominee is not available for election.

General Information About the Nominees. All of the nominees are currently Directors of the Company. Each of the nominees has agreed to be named in the proxy statement and to serve as a Director if elected.

NOMINEES FOR DIRECTOR

<Table>
<Caption>

NAME	CURRENT POSITION WITH
<S>	<C>
Andrew G. Bodnar, M.D.(3)(4).....	Director
Vincent T. DeVita, Jr., M.D.(5)(6).....	Director
Robert F. Goldhammer(3)(4)(6).....	Chairman of the Boar
David M. Kies(2)(4)(6).....	Director
Paul B. Kopperl(1)(2)(4)(6).....	Director
Arnold J. Levine, Ph.D.(4)(5)(6).....	Director
John Mendelsohn, M.D.(5)(6).....	Director
William R. Miller(1)(2)(3)(4)(6).....	Director
Peter S. Ringrose, Ph.D.(5).....	Director
Harlan W. Waksal, M.D.(3)(5).....	Executive Vice Presi Operating Officer an
Samuel D. Waksal, Ph.D.(3)(5).....	President, Chief Exe and Director

</Table>

(1) Member of Audit Committee

(2) Member of Compensation and Stock Option Committee

(3) Member of Executive Committee

(4) Member of Nominating and Corporate Governance Committee

(5) Member of Research Oversight Committee

(6) Member of Special Committee

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BUSINESS EXPERIENCE OF NOMINEES FOR DIRECTOR

ANDREW G. BODNAR, M.D., 54, has been a Director of the Company since November 2001. Dr. Bodnar was designated and is being nominated as a Director pursuant to a Stockholder Agreement, dated as of September 19, 2001, among the Company, Bristol-Myers Squibb Company and Bristol-Myers Squibb Biologics Company. Dr. Bodnar is Senior Vice President, Medical and External Affairs of Bristol-Myers Squibb. Previously, Dr. Bodnar served as President, Oncology/Immunology and Worldwide Strategic Business Development for Bristol-Myers Squibb's Pharmaceutical Group. Prior to joining Bristol-Myers Squibb, Dr. Bodnar was Associate Chief of Internal Medicine, Acting Chief of Cardiology and Director of the Internal Medicine Residency Program at Massachusetts General Hospital in Boston. Dr. Bodnar serves on the Board of Trustees of The New York Blood Center, The Fox Chase Cancer Center and The

American Boychoir School.

VINCENT T. DEVITA, JR., M.D., 67, has been a Director of the Company since February 1992. Since 1993, Dr. DeVita has served as Director of the Yale Cancer Center as well as Professor of Medicine and Professor of Epidemiology and Public Health at Yale University School of Medicine, New Haven, Connecticut. From September 1988 through June 1995, Dr. DeVita served as Attending Physician at Memorial Sloan-Kettering Cancer Center ("Sloan Kettering"), New York, and through June 1991 as Physician-in-Chief. From 1980 to 1988, he served under Presidential appointment as Director of the National Cancer Institute ("NCI"), where he had held various positions since 1966. During his years with the NCI, Dr. DeVita was instrumental in developing the first successful combination cancer chemotherapy program. This work ultimately led to effective regimens of curative chemotherapy for a variety of cancers. Dr. DeVita's numerous awards include the 1990 Armand Hammer Cancer Prize and the 1982 Albert and Mary Lasker Medical Research Award for his contribution to the cure of Hodgkin's disease. Dr. DeVita received his M.D. from the George Washington University School of Medicine, Washington, D.C. in 1961.

ROBERT F. GOLDHAMMER, 71, has served as the Company's Chairman of the Board since February 1991 and has been a Director of the Company since October 1984. Mr. Goldhammer was the Vice Chairman of the Executive Committee of the Board of Directors of Kidder, Peabody & Company where he was employed from 1956 to 1989. While at Kidder, he was also Chairman of the Boston Stock Exchange (1969-1972), a member of the Board of Governors of the Investment Bankers Association (1967) and the Chairman of the New England Group ISA (1966-1967). He has been since 1991, a partner of Concord International Group, L.P. He serves as a director on the Boards of Esterline Corporation and Community Connect Incorporated. Mr. Goldhammer has served as a trustee of the Episcopal Diocese of Massachusetts. He also served as a trustee of Boston University and the Kennedy Center of Performing Arts in Washington D.C. Throughout his career, Mr. Goldhammer has advised numerous firms in the area of fundraising, operations, marketing, finance, strategy and management. He is a graduate of Boston University.

DAVID M. KIES, 58, has been a Director of the Company since June 1996. Mr. Kies is a Partner of the New York based law firm Sullivan & Cromwell, specializing in mergers and acquisitions, securities and general corporate matters.

PAUL B. KOPPERL, 68, has been a Director of the Company since December 1995. He has served as President of Delano & Kopperl, Inc., a private business strategy and venture investing firm in Boston and its predecessor firms from 1976 to the present. In 2001, Mr. Kopperl retired as President but remains a director of Pegasus Investments, Inc., a private investment management firm in Boston. From 1967 through 1975, he was Vice President and a principal of Kidder, Peabody & Co. Incorporated, New York, an investment banking firm. From 1959 to 1967 he was an associate with Goldman, Sachs & Co., New York. Mr. Kopperl is a Trustee of the Dana-Farber Cancer Institute, Boston, a member of its Executive, Investment and Trustee Science Committees and a Trustee of Dana-Farber/Children's Hospital Cancer Care, Inc. He is a director of Centagenetix, Inc., Cambridge, Massachusetts, serves as Advisor to the Dean, Harvard School of Public Health, and is a visiting lecturer at the United States Military Academy, West Point. Over the years he has served as a trustee or director of numerous businesses and not-for-profit educational, performing arts and social welfare organizations.

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ARNOLD J. LEVINE, PH.D., 62, has been a Director of the Company since April 2000. Dr. Levine is a cancer biologist and was President of Rockefeller University from November 1998 to January 2002. Previously, Dr. Levine was the Harry C. Wiess Professor of Life Sciences at Princeton University, where he founded Princeton's molecular biology department during a 12-year tenure that saw the department grow to include two research laboratories and 35 faculty members. Prior to his work at Princeton, Dr. Levine was Chairman at SUNY Stony Brook School of Medicine. Dr. Levine is also a Director of Applera Corporation, Advanced Medicine and Infinity Pharm.

JOHN MENDELSOHN, M.D., 65, has been a Director of the Company since February 1998. He has served as the President of M.D. Anderson Cancer Center, University of Texas, where he has also been Professor of Medicine since 1996. From 1985 to 1996 he was Chairman of the Department of Medicine at Sloan Kettering, New York, as well as holder of the Winthrop Rockefeller Chair in Medical Oncology at Sloan Kettering. He was also Professor and Vice-Chairman of Medicine at Cornell University Medical College and an attending physician at both Memorial and New York Hospitals. Dr. Mendelsohn served on the faculty of the University of California, San Diego and was instrumental in the creation of the University's Cancer Center, where he served as Director from 1976 to 1985. Dr. Mendelsohn's work has focused on growth factors and their role in regulating the proliferation of cancer cells through cell surface receptors. Dr. Mendelsohn was responsible for developing specific monoclonal antibodies that block receptors, including epidermal growth factor receptors, which mediate growth factor activation of cell growth and division. Dr. Mendelsohn is currently a board member of Enron Corp. and the Greater Houston Partnership and is a fellow of the New York Academy of Medicine. In 1997, Dr. Mendelsohn was elected to the Institute of Medicine of the National Academy of Sciences.

WILLIAM R. MILLER, 73, has been a Director of the Company since June 1996. Mr. Miller served as Vice Chairman of the Board of Directors of the Bristol-Myers Squibb Company from 1985 until 1991, at which time he retired. Mr. Miller is a director of Isis Pharmaceuticals, Inc. and Transkaryotic Therapies, Inc. He is Chairman of the Board of Vion Pharmaceuticals, Inc. He is Chairman of the Board of Trustees of the Cold Spring Harbor Laboratory and is a past Chairman of the Board of the Pharmaceutical Manufacturers Association. Mr. Miller is a Trustee of the Manhattan School of Music, Metropolitan Opera Association and Opera Orchestra of New York. He is a member of Oxford University Chancellor's Court of Benefactors, Honorary Fellow of St. Edmund Hall and Chairman of the English-Speaking Union of the United States.

PETER S. RINGROSE, PH.D., 56, has been a Director of the Company since November 2001. Dr. Ringrose was designated and is being nominated as a Director pursuant to a Stockholder Agreement, dated as of September 19, 2001, among the Company, Bristol-Myers Squibb Company and Bristol-Myers Squibb Biologics Company. Dr. Ringrose is President of the Bristol-Myers Squibb Pharmaceutical Research Institute, and, since January 2000, has been Chief Scientific Officer of Bristol-Myers Squibb. Dr. Ringrose joined Bristol-Myers Squibb in January 1997 from Pfizer where he was Senior Vice President, Worldwide Discovery and Medicinal Research and Development, Europe, based in Sandwich, UK. Dr. Ringrose is a member of the advisory board for the Centre for Medicines Research in the UK. He is a member of the Science & Regulatory Section executive Committee for PhRMA (Pharmaceutical Research and Manufacturers of America) and is currently Chairman-Elect of the Section. He is Chairman of the Hever Group of pharmaceutical R&D heads, and he sits on the U.S. Council on Competitiveness. In addition, Dr. Ringrose has been appointed to the Chancellor's Court of Benefactors at the University of Oxford.

HARLAN W. WAKSAL, M.D., 49, is a founder of the Company and has been a Director since April 1984. He has directed the Company's research and

development since April 1985, and has served as the Company's Executive Vice President and Chief Operating Officer since March 1987. From 1985 to March 1987, Dr. Waksal served as the Company's President. Dr. Waksal received his training in Internal Medicine from Tufts-New England Medical Center Hospital and in Pathology from Kings County Hospital in Brooklyn, New York from 1982 to 1987. From 1984 to 1985, Dr. Waksal was Chief Resident in Pathology at Kings County Hospital. He received his Medical Degree from Tufts University School of Medicine in 1979. He is currently Adjunct Assistant Professor in the Department of Pathology at Downstate Medical Center, New York. Dr. Harlan W. Waksal and Dr. Samuel D. Waksal are brothers.

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SAMUEL D. WAKSAL, PH.D., 54, President and Chief Executive Officer of the Company, is a founder of the Company and has been its Chief Executive Officer and a Director since August 1985 and President since March 1987. From 1982 to 1985, Dr. Waksal was a member of the faculty of Mt. Sinai School of Medicine as Associate Professor of Pathology and Director of the Division of Immunotherapy within the Department of Pathology. He has served as visiting Investigator of the National Cancer Institute, Immunology Branch, Research Associate of the Department of Genetics, Stanford University Medical School, Assistant Professor of Pathology at Tufts University School of Medicine and Senior Scientist for the Tufts Cancer Research Center. Dr. Waksal was a scholar of the Leukemia Society of America from 1979 to 1984. Dr. Waksal has been a visiting professor at the Weizmann Institute in Israel and the Pasteur Institute in France. Dr. Waksal currently serves on the Executive Committee of the New York Biotechnology Association, the Board of Advisors of Rockefeller University and is Chairman of the New York Council for the Humanities. Dr. Waksal sits on the Board of Antigenics Inc. Dr. Samuel D. Waksal and Dr. Harlan W. Waksal are brothers.

THE BOARD RECOMMENDS A VOTE "FOR" EACH OF THE NOMINEES NAMED ABOVE (PROPOSAL NO. 1 ON YOUR PROXY CARD).

DIRECTORS' COMPENSATION

CASH COMPENSATION

Exclusive of the Chairman of the Board, each non-employee Director of the Company for 2001 received compensation of $10,000 per year, or a pro rata portion thereof for persons not serving the full fiscal year, for such person's services as a Director as well as reimbursement of the Director's reasonable out-of-pocket expenses incurred in connection with his Board and Board committee activities. This annual compensation was raised to $30,000 for 2002. The Chairman of the Board receives $150,000 per year for his services as Chairman as well as reimbursement of his reasonable out of pocket expenses incurred in connection with his Board and Board committee activities. In addition, the Chairman of each of the Board committees, exclusive of the Chairman of the Board, receives $5,000 per year as compensation for services as committee Chairman. This fee was raised to $10,000 for 2002. Dr. DeVita did not receive compensation for his service as a Director during 2001 due to his consulting arrangement with the Company during 2001, which consulting arrangement has been terminated. See "Certain Relationships and Related Transactions."

DIRECTORS' STOCK OPTIONS

Pursuant to the Company's 1996 Non-Qualified Stock Option Plan (the "1996 Non-Qualified Plan"), each Director who is not an employee of the Company automatically receives on each February 15th an option to purchase 30,000 shares

of common stock except that the Chairman of the Board receives an option to purchase 60,000 shares. Each individual joining the Board within the first nine months of the year receives a pro rata portion thereof. Such options vest after one full year of service on the Board from the date of grant and have an exercise price equal to the fair market value of the common stock on the date of grant. Each Director newly joining the Board who is not an employee of the Company is made a one-time option grant under the 1996 Non-Qualified Plan to purchase 50,000 shares of common stock. Such options vest as to 25% of the shares of common stock over the four-year period commencing with the date of grant, subject to such individual's continued service on the Board on the scheduled date of vesting, and have an exercise price equal to the fair market value of the common stock on the date of grant. To the extent there is not capacity under the Company's 1996 Non-Qualified Plan, these grants may come from the Company's 1998 Non-Qualified Stock Option Plan. From time to time, Directors who are not employees of the Company may be granted additional options in consideration for providing services on the Board. No such additional grants were made during 2001. If Proposal No. 2 in this proxy statement, "Approval of the ImClone Systems Incorporated 2002 Stock Option Plan," is approved, Directors will no longer receive automatic option grants on each February 15th, but it is expected that they will continue to receive comparable grants on a discretionary basis.

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The table below sets forth option grants to Directors who are not employees of the Company made during the year ended December 31, 2001 in consideration for such Directors serving on the Board:

<Table>
<Caption>

NAME	NUMBER OF OPTIONS
<S>	<C>
Andrew G. Bodnar	50,000(2)
Vincent T. DeVita, Jr.	30,000(1)
Robert F. Goldhammer	60,000(1)
David M. Kies	30,000(1)
Paul B. Kopperl	30,000(1)
Arnold J. Levine	30,000(1)
John Mendelsohn	30,000(1)
William R. Miller	30,000(1)
Peter S. Ringrose	50,000(2)

</Table>

(1) These options were granted automatically pursuant to the terms of the 1996 Non-Qualified Plan on February 15, 2001 at a per share exercise price of $37.1875, which is equal to the fair market value of the common stock on the date of grant. The options vested and became exercisable in their entirety on February 15, 2002 and will terminate on February 14, 2011.

(2) In accordance with Company policy, upon joining the Board of Directors on November 15, 2001, Dr. Bodnar and Dr. Ringrose were each granted options to purchase 50,000 shares at a per share exercise price of $62.07, which is equal to the fair market value of the common stock on the date of grant. These options vest as to 25% of the shares of common stock over the four-year period commencing with the date of grant, subject to such individual's continued service on the Board of Directors on the scheduled

date of vesting.

INFORMATION CONCERNING BOARD AND COMMITTEE
MEETINGS AND COMMITTEES OF THE BOARD

The Board of Directors oversees the business and affairs of the Company and monitors the performance of management. In accordance with corporate governance principles, the Board does not involve itself in day-to-day operations. During the year ended December 31, 2001, there were twelve meetings of the Company's Board. The Board also took certain actions by unanimous written consent. No incumbent Director attended fewer than 75% of the total number of meetings of the Board and of the Committees of the Board on which he served.

The Company has an Executive Committee of the Board currently composed of Samuel D. Waksal (Chairman), Andrew G. Bodnar, Robert F. Goldhammer, William R. Miller and Harlan W. Waksal. The Executive Committee acts for the Board when formal Board action is required between Board meetings. The Executive Committee has all the power of the full Board in the management of the business and affairs of the Company, except those powers that by law cannot be delegated by the Board. The Executive Committee met twice during the year ended December 31, 2001.

The Company has an Audit Committee of the Board currently composed of Paul B. Kopperl (Chairman) and William R. Miller. The Board expects to appoint an additional member to the Audit Committee at its next Board meeting. Each of the members of the Audit Committee is an "independent director" as defined in Rule 4200 of the listing standards of the National Association of Securities Dealers, Inc. The Audit Committee operates under a written charter, a copy of which was attached as Appendix A to the Company's proxy statement for its 2000 fiscal year. The primary functions of the Audit Committee are to monitor the integrity of the Company's financial reporting process and systems of internal controls regarding finance, accounting and, with certain exceptions, legal compliance. The Audit Committee provides an avenue of communication among the independent auditors, management and the Board of Directors. The Audit Committee met three times during the year ended December 31, 2001.

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The Company has a Compensation and Stock Option Committee (the "Compensation Committee") of the Board currently composed of William R. Miller (Chairman), David M. Kies and Paul B. Kopperl. The Compensation Committee is responsible for developing executive compensation policies. The Compensation Committee also (i) determines annually the base salary to be paid to the Chief Executive Officer and determines bonuses and incentive awards to be paid from time to time to the Chief Executive Officer; and (ii) approves annually a salary plan for other senior officers (on the recommendation of the Chief Executive Officer in conjunction with other senior personnel) and approves bonuses and incentive awards to be paid from time to time to such senior officers. The Compensation Committee also administers the Company's various stock option and purchase plans, including the granting of options under the option plans. The Compensation Committee met twice during the year ended December 31, 2001 and also took certain actions by unanimous written consent.

The Company has a Nominating and Corporate Governance Committee currently composed of David M. Kies (Chairman), Andrew G. Bodnar, Robert F. Goldhammer, Paul B. Kopperl, Arnold J. Levine and William R. Miller. The Nominating and Corporate Governance Committee considers and makes recommendations to the Board regarding Board and committee nominees and

membership, director performance and officer candidates. The Nominating and Corporate Governance Committee also considers and makes recommendations to the Board with respect to corporate organizational and governance matters. The Nominating and Corporate Governance Committee met one time during the year ended December 31, 2001. The Nominating and Corporate Governance Committee considers nominations for director made by stockholders of the Company in accordance with the procedures for submission of proposals at annual or special meetings of stockholders set forth in the Company's Amended and Restated By-laws.

The Company has a Research Oversight Committee currently composed of Samuel D. Waksal (Chairman), Vincent T. DeVita, Jr., Arnold J. Levine, John Mendelsohn, Peter S. Ringrose and Harlan W. Waksal. The Research Oversight Committee participates on behalf of the Board in monitoring the research focus of the Company. The Research Oversight Committee did not meet formally during the year ended December 31, 2001.

In February 2002, the Board of Directors established a Special Committee. The Special Committee is currently composed of Vincent T. DeVita, Jr., Robert F. Goldhammer, David M. Kies, Paul B. Kopperl, Arnold J. Levine, John Mendelsohn and William R. Miller. The Special Committee has been delegated all lawful authority of the Board in connection with the investigation of the SEC into possible violations of the federal securities laws by the Company and certain unnamed individuals, the subpoena from a grand jury sitting in the United States District Court for the Southern District of New York related to an investigation by the United States Department of Justice, the inquiry of the Oversight and Investigations Subcommittee of the House Energy and Commerce Committee into the conduct of the Company in the development of the Company's product candidate, ERBITUX(TM), federal securities actions naming the Company and certain Directors as defendants, stockholder derivative actions, a proposal from BMS on February 5, 2002 which sought to restructure the relationship between the Company and BMS, which has subsequently been resolved through the amendment of the agreement between the Company and BMS dated March 5, 2002, and any matters that may arise in the future based upon the same or similar facts or allegations.

EXECUTIVE COMPENSATION

INFORMATION CONCERNING EXECUTIVE OFFICERS

Certain information concerning executive officers of the Company is provided below.

SAMUEL D. WAKSAL, PH.D., is the President and Chief Executive Officer of the Company. Certain information concerning Dr. Waksal appears on page 9.

HARLAN W. WAKSAL, M.D., is the Executive Vice President and Chief Operating Officer of the Company. Certain information concerning Dr. Waksal appears on page 8.

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PETER BOHLEN, PH.D., 59, has been Senior Vice President, Research of the Company since January 2001. He joined the Company as Vice President, Research in September 1996 and served in that capacity through December 2000. From November 1995 to July 1996 he was Senior Director of Ixsys, a privately-held biotechnology company. From October 1987 to June 1996 he was department head of the Molecular Biology Section of American Cyanamid's Medical Research Division and director of the company's angiogenesis program. He also has held academic positions at the Salk Institute, San Diego and the University of Zurich,

Switzerland. Dr. Bohlen received his Ph.D. in chemistry from the University of Berne in Switzerland. In 1983, he received the Cloetta Award in Switzerland for his contributions in the field of protein analysis. He has authored or co-authored over 200 publications and is a named inventor on 26 patents.

CHARLES DUNNE, 37, has been Vice President, Management Information Systems and Facilities since January 2001. Mr. Dunne, one of the Company's first employees, joined the Company in 1984 and has served it in a number of capacities, including Assistant Vice President, Management Information Systems and Facilities during 2000, Senior Director, Management Information Systems during 1999 and Director, Management Information Systems during 1998. Mr. Dunne supervised the construction of the Company's corporate headquarters and research laboratories and has implemented all systems at the Company since 1984.

PAUL A. GOLDSTEIN, 37, has been Vice President, Financial Operations since January 2001. He joined the Company in January 1992 and has served in various capacities since that date, including Assistant Vice President, Finance during 2000, Senior Director, Finance and Controller from January 1998 through December 1999 and Controller from January 1995 through December 1997. Prior to joining the Company he was employed by Laventhol & Horwath, a certified public accounting firm in New York City. Mr. Goldstein is a certified public accountant.

MICHAEL HOWERTON, 50, has served as the Company's Vice President, Business Development since August 2001. Mr. Howerton is responsible for the pursuit and development of new business opportunities for the Company, including acquisitions, product in-licensing and out-licensing and strategic alliances. Prior to joining the Company, Mr. Howerton built a 25-year career at Bristol-Myers Squibb Company. In his most recent position at Bristol-Myers Squibb, Mr. Howerton served as Vice President, Financial Analysis and Assistant Controller from 1998 to 2001, directing activities relating to the financial and strategic analysis, budgeting and profit planning of the Company. Prior to this position, Mr. Howerton served as Vice President, Corporate Development for eight years, and was responsible for activities relating to the acquisitions, divestitures and strategic alliances for the Company's Worldwide Medicine Group.

JOHN B. LANDES, 54, has served as Senior Vice President, Legal since January 2001. He was Vice President, Legal from 1992 to 2000; Vice President, Business Development from 1992 through 1999 and General Counsel from 1992 through 2002. Prior thereto, he was Vice President, Administration and Legal since December 1984. He was Secretary of the Company from April 1985 through February 2002 and served as its Treasurer from April 1984 through September 1991, except for an interim period from December 1988 to February 1991. From 1978 to 1984, Mr. Landes was an associate attorney with the Boston law firm of Mahoney, Hawkes and Goldings.

LILY WAIYEE LEE, PH.D., 46, joined the Company in April 2001 as its Vice President, Regulatory Affairs and Biostatistics. Dr. Lee was employed at The Lipsome Company, Division of Elan Corporation, as its Vice President, Clinical & Regulatory Operations and Biostatistics from 1995 to April 2001 and as its Executive Director, Biostatistics and Data Management from 1993 through 1994. Prior to that time she was employed for over eight years in various statistical positions at Ciba Consumer Pharmaceuticals, Division of Ciba Geigy and at Janssen Pharmaceutica, a division of Johnson & Johnson. Dr. Lee earned a bachelor degree in statistics from the University of Minnesota and both a masters degree in Biostatistics and Ph.D. in Demography from the University of California, Berkeley.

DANIEL S. LYNCH, 44, joined the Company in April 2001 as its Vice President, Finance and Chief Financial Officer. In September 2001, he was

promoted to Senior Vice President, Finance and in February 2002 was appointed Secretary of the Company. From May 1999 through March 2001, he served as Chief Financial Officer of Derby Cycle Corporation. Prior to this, Mr. Lynch served for 15 years in various

capacities at Bristol-Myers Squibb Company, including from December 1998 through May 1999, as its Vice President, Finance, U.S. Pharmaceutical, Worldwide Medicines Group; from April 1998 through November 1998 as its Vice President, Finance, Technical Operations, Worldwide Medicines Group; from July 1997 through March 1998 as its Vice President, Finance, Intercontinental, Worldwide Medicines Group; and from February 1995 through June 1997 as its Vice President, Finance, Worldwide Consumer Medicines Group.

RONALD A. MARTELL, 40, has served as the Company's Vice President, Marketing and Sales since November 1998. Prior to joining the Company he worked at Genentech, Inc. for ten years where he held various positions. Most recently, from 1996 until joining the Company, he served as Genentech's Group Manager of Oncology Products where he directed the launch of Herceptin, Genentech's monoclonal antibody product approved to treat breast cancer. From 1995 to 1996 he served as Senior Product Manager where he launched Pulmozyme for cystic fibrosis in Europe. From 1994 through 1995 he served as Manger of Genentech's Piedmont Sales Division. Prior to that, he served from 1993 as Associate Product Manager for Genentech's Pulmozyme.

MICHAEL NEEDLE, M.D., 42, has served as the Company's Vice President, Clinical Affairs since January 2001. He joined the Company in April 2000 as its Assistant Vice President, Clinical Affairs. Prior to joining the Company, Dr. Needle served as Director, Oncology Clinical Research of G.D. Searle, a Monsanto Company. From July 1993 through November 1997 Dr. Needle served as Assistant Professor of Pediatrics and Neurology, Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine. Dr. Needle received a Bachelor of Arts degree in Physics from Binghamton University and a Doctor of Medicine degree from the State University of New York, Health Science Center at Brooklyn. Dr. Needle performed his residency in Pediatrics at Kings County Hospital in Brooklyn and his Pediatric Hematology/Oncology fellowship at the Fred Hutchinson Cancer Research Center in Seattle and the University of Texas, MD Anderson Cancer Center in Houston.

ANDREA F. RABNEY, 35, has served as the Company's Vice President, Corporate Communications since January 2001. She joined the Company in 1993 as its Director, Corporate Development and Investor Relations and has served in several other managerial positions since that time, including Senior Director, Corporate Development & Investor Relations from 1998 to 1999 and Assistant Vice President, Corporate Communications during 2000. Prior to joining the Company, Ms. Rabney served as a compliance analyst at Smith Barney Shearson Inc. (now Salomon Smith Barney) where she was responsible for defining capital markets guidelines and procedures for foreign and institutional accounts and trading desks. Ms. Rabney holds a law degree from the Jacob D. Fuchsberg Law Center of Touro College.

CLIFFORD R. SAFFRON, 44, joined the Company on February 1, 2002, as Vice President, Legal -- Special General Counsel. From February 1, 1994 through November 30, 2001, he was Senior Vice President -- Deputy General Counsel of ICN Pharmaceuticals, Inc. Prior to this, from October 1989 through January 1994, he was a litigation associate with the law firm of Proskauer Rose LLP in its New York City office.

S. JOSEPH TARNOWSKI, PH.D., 48, has served as the Company's Senior Vice

April 2001. Prior to joining the Company, he held various positions with CellPro, Inc., the principal business of which was the development, manufacture and marketing of automated systems that utilize monoclonal antibodies to purify large quantities of specific cells for therapeutic and diagnostic applications. He joined CellPro in June 1992 as Vice President of Operations, was appointed to Vice President of Research and Development in June 1995 and became Senior Vice President and Chief Technical Officer in December 1996. From November 1986 to May 1992, Dr. Tarnowski was Director, Process and Product Development of Scios Nova Inc. (formerly California Biotechnology Inc.), a company that develops recombinant human proteins for therapeutic uses. Dr. Tarnowski received a Ph.D. in Biochemistry from the University of Tennessee in 1979 and was a Postdoctoral Fellow at the Roche Institute of Molecular Biology from 1979 through 1981.

CATHERINE M. VACZY, 40, has served as the Company's Associate General Counsel since February 1997 and Vice President, Legal since January 2001. She served as its Assistant Vice President, Legal

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during 2000 and as its Senior Director, Legal, from 1997 through 1999. Prior to joining the Company, Ms. Vaczy served as a senior associate specializing in corporate and securities matters in the New York City office of Ross & Hardies, a Chicago-based law firm.

EMPLOYMENT AGREEMENTS

EMPLOYMENT AGREEMENTS WITH NAMED EXECUTIVE OFFICERS. On September 19, 2001, Samuel D. Waksal, Harlan W. Waksal, Daniel S. Lynch and S. Joseph Tarnowski entered into employment agreements with the Company to be effective as of the date thereof (the "Commencement Date"). The period of employment, during which salary, bonus and benefits shall be provided to Dr. Samuel D. Waksal, Dr. Harlan W. Waksal, Mr. Lynch and Dr. Tarnowski began on the Commencement Date and will end on the third anniversary thereof (the "Term"); provided, that, with respect to Dr. Samuel D. Waksal and Dr. Harlan W. Waksal, the Term shall automatically be extended for one additional day each day, unless a notice not to extend is provided.

SAMUEL D. WAKSAL. Pursuant to the employment agreement with Dr. Waksal, he shall serve as the President and Chief Executive Officer and as a member of the Board of Directors. Dr. Waksal's base salary is required to be not less than $500,000 and he will be eligible to receive an annual bonus; provided, that, the annual bonus shall not be less than $1,000,000 less his base salary for the relevant year.

Dr. Waksal will be entitled to participate in customary employee benefit plans and programs sponsored by the Company. In addition, the Company will reimburse Dr. Waksal for up to $15,000 annually for personal tax planning and financial advice and will provide him with a term life insurance policy with a death benefit of at least $5,000,000. On the Commencement Date, pursuant to the terms of the employment agreement, Dr. Waksal was granted a ten year stock option to acquire 1,250,000 shares of the Company's common stock at an exercise price per share equal to $50.01, the fair market value at the time of the grant. The stock option will vest as to 100% of the shares subject thereto on the third anniversary of the date of grant; provided, that, 33 1/3% of the shares subject to the stock option will each automatically vest when the Company's ten day average stock price reaches $60, $80 and $100 per share, respectively. In addition, the stock option shall become 100% vested upon a "change in control" of the Company. These options vested as to the first 33 1/3% on October 31,

2001.

If Dr. Waksal's employment is terminated by the Company without "cause" or by Dr. Waksal for "good reason," Dr. Waksal will be paid or provided, in addition to accrued but unpaid compensation and benefits and pro-rata bonus, a (a) lump-sum cash payment equal to three times the sum of his base salary and highest bonus paid in last three years (with highest bonus paid deemed to be at least two times his then current base salary); (b) continuation of health and welfare benefits for three years; (c) immediate vesting of all stock-based awards, including the stock options discussed above and all outstanding options shall remain exercisable until the remainder of their term regardless of any termination of employment provisions therein contained; (d) lump sum payment equal to the present value of the Company's contributions which would have been made under all of the Company's retirement plans if he had continued to be employed by the Company for an additional three years and (e) payment by the Company of all contributions or payments for the year of termination under all insurance benefits or policies for the benefit of Dr. Waksal of which he shall become the owner.

If any of the payments to be made to Dr. Waksal could result in the imposition of an excise tax under Section 4999 of the Internal Revenue Code of 1986, as amended (the "Code"), the Company shall pay Dr. Waksal an additional amount to fully gross him up for such taxes, unless, by reducing the amounts payable to him by 10%, no amounts would be subject to the excise tax, in which case the payments shall be so reduced.

The employment agreement contains confidentiality, non-competition and non-solicitation provisions.

For purposes of the employment agreement, the Company will have "cause" to terminate Dr. Waksal upon (a) a final conviction or plea of guilty or no contest to a felony involving moral turpitude or (b) willful misconduct that is materially and demonstrably injurious economically to the Company. Among

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other events, Dr. Waksal will have "good reason" to terminate his employment with the Company (a) if there is any material and adverse change in his duties or responsibilities, (b) if there is a reduction in his base salary, bonus opportunity, or any material benefit, (c) for any reason during the thirty-day period following the first anniversary of a change in control of the Company, (d) if the Company provides a notice of non-renewal of the Term, (e) if he is required to relocate or (e) if there is a breach of any material provision of the employment agreement by the Company.

HARLAN W. WAKSAL. Dr. Waksal's employment agreement with the Company is substantially the same as the employment agreement with Dr. Samuel D. Waksal except that: (a) he will serve as Executive Vice President and Chief Operating Officer and as a member of the Board of Directors, (b) his base salary is required to be not less than $455,000 per year and (c) he was granted stock options to acquire 1,000,000 shares of the Company's common stock.

DANIEL S. LYNCH. Mr. Lynch's employment agreement is substantially the same as the employment agreement with Dr. Samuel D. Waksal except that: (a) he will serve as Senior Vice President and Chief Financial Officer, (b) the Term of his agreement does not automatically renew, (c) his base salary is required to be not less than $360,000 and his minimum guaranteed bonus is $360,000, (d) he was granted stock options to acquire 200,000 shares of the Company's common stock which vest as to 33 1/3% of the shares subject thereto on each of the first three anniversaries of the date of grant, and (e) upon a termination of

his employment by the Company without "cause" or by Mr. Lynch for "good reason," his bonus is deemed to be no less than $360,000. In addition, among other events, Mr. Lynch will have "good reason" to terminate his employment with the Company (a) if there is any material and adverse change in his duties or responsibilities, (b) if there is a reduction in his base salary, bonus opportunity, or any material benefit, (c) if he is required to relocate or (d) if there is a breach of any material provision of the employment agreement by the Company.

S. JOSEPH TARNOWSKI. Dr. Tarnowski's employment agreement is substantially the same as the employment agreement with Dr. Samuel D. Waksal except that: (a) he will serve as Senior Vice President -- Manufacturing Operations and Product Development, (b) the Term of his agreement does not automatically renew, (c) his base salary is required to be not less than $225,000 and his minimum guaranteed bonus is $100,000, (d) he was not granted stock options and (e) upon a termination of his employment by the Company without "cause" or by Dr. Tarnowski for "good reason," his bonus is deemed to be no less than $100,000. In addition, among other events, Dr. Tarnowski will have "good reason" to terminate his employment with the Company (a) if there is any material and adverse change in his duties or responsibilities, (b) if there is a reduction in his base salary, bonus opportunity, or any material benefit, (c) if he is required to relocate or (d) if there is a breach of any material provision of the employment agreement by the Company.

REPORT OF THE COMPENSATION COMMITTEE

This Report was adopted by the Compensation Committee on April 3, 2002, at which time the Directors signing this Report constituted the Compensation Committee membership. Subsequent to the adoption of this Report, William R. Miller joined the Compensation Committee, replacing Robert F. Goldhammer as Chairman. During 2001, Richard Barth and Peter S. Ringrose also served on the Compensation Committee. Dr. Ringrose resigned from the Compensation Committee on March 19, 2002, and Mr. Barth resigned from the Board of Directors on April 2, 2002.

Overall Philosophy

The Company's executive compensation philosophy is based on the premise that compensation should be set at levels that support the Company's business strategies and long-term objectives and relate to an individual's performance. The elements of the executive compensation package are base salary and participation in annual incentives, including stock options.

In establishing base salaries, annual incentive awards and awards of stock options, the Compensation Committee considers the executive's annual review and periodic compensation surveys, including those provided by third parties covering the biopharmaceutical industry.

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The Compensation Committee uses no set formulas and may accord different weight to different factors for each executive. The Committee looks toward the progress of the Company's research and development programs, its ability to gain support for such programs, either internally or externally, its ability to attract, motivate and retain talented employees and its ability to secure capital sufficient for its product development to achieve rapid and effective commercialization as may be practicable.

Deductibility of Compensation

The Compensation Committee has reviewed the impact of Section 162(m) of the Internal Revenue Code of 1986, as amended (the "Code"), which, beginning in 1994, limits the deductibility of certain otherwise deductible compensation in excess of $1 million paid to the Chief Executive Officer and the other Named Executive Officers (as defined). It is the policy of the Company to attempt to have its executive compensation plans treated as deductible compensation whenever, in the judgment of the Compensation Committee, to do so would be consistent with the objectives of that compensation plan.

Chief Executive Officer Compensation

Dr. Samuel D. Waksal's base salary was fixed in January 2001 at $550,000 and represented an increase of 10% over his 2000 base salary. Dr. Waksal and the Company entered into an employment agreement on September 19, 2001. Also on this date, the Company entered into its strategic partnership with Bristol-Myers Squibb Company ("BMS"). Under the employment agreement, Dr. Waksal was granted options to purchase 1,250,000 shares of the Company's common stock at an exercise price of $50.01 per share. The options vest after three years but are subject to earlier vesting should certain targets be attained in the Company's stock price. Dr. Waksal's employment agreement provides for a guaranteed minimum annual bonus that is not less than the difference between $1,000,000 and his base salary for the relevant bonus year. Accordingly, Dr. Waksal was paid a bonus for 2001 of $450,000. This was paid in 2002. Dr. Waksal was paid no discretionary bonus for 2001.

Compensation and Stock Option Committee

Robert F. Goldhammer, Chairman
David M. Kies
Paul B. Kopperl

The foregoing Report of the Compensation Committee shall not be deemed to be soliciting material, to be filed with the SEC or to be incorporated by reference into any of the Company's previous or future filings with the SEC, except as otherwise explicitly specified by the Company in any such filing.

COMPENSATION COMMITTEE INTERLOCKS AND INSIDER PARTICIPATION

During the fiscal year ended December 31, 2001, the following Board members served on the Compensation Committee: Robert F. Goldhammer, Richard Barth, David M. Kies, Paul B. Kopperl and Peter S. Ringrose, none of whom is an employee of the Company or any of its subsidiaries or has ever been an executive officer of the Company or any subsidiaries. Dr. Ringrose resigned from the Compensation Committee on March 19, 2002, and Mr. Barth resigned from the Board on April 2, 2002. Dr. Ringrose is an executive officer of BMS. In 2001, the Company accepted a promissory note from Mr. Goldhammer. See "Certain Relationships and Related Transactions" for descriptions of the Company's relationship with BMS and the terms of the Company's promissory note from Mr. Goldhammer.

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SUMMARY COMPENSATION TABLE

The Summary Compensation Table sets forth the cash and non-cash compensation awarded to, earned by, or paid to the Company's Chief Executive Officer and the four most highly compensated executive officers (other than the

Chief Executive Officer) for the years ended December 31, 2001, 2000 and 1999 who were serving as executive officers at December 31, 2001 and whose total salary and bonus exceeded $100,000 for the year ended December 31, 2001 (the "Named Executive Officers").

<Table>
<Caption>

		ANNUAL COMPENSATION			
NAME AND PRINCIPAL POSITION	YEAR	SALARY(1) ($)	BONUS(2) ($)	OTHER ANNUAL COMPENSATION(3)	SECU
<S>	<C>	<C>	<C>	<C>	<C>
Samuel D. Waksal.....	2001	$550,000	$ 450,000	$ --	
President and Chief	2000	500,000	1,000,0000	--	
Executive Officer	1999	300,000	600,000	--	
Harlan W. Waksal.....	2001	451,404	545,000(8)	--	
Executive Vice	2000	400,000	800,000	--	
President and Chief	1999	250,000	500,000	--	
Operating Officer					
Daniel S. Lynch(9).....	2001	223,769	525,000(10)	--	
Senior Vice President,					
Finance and Chief					
Financial Officer					
S. Joseph Tarnowski.....	2001	217,808	225,000	--	
Senior Vice President,	2000	204,750	100,000	36,083(14)	
Manufacturing	1999	195,000	60,000	--	
Operations and					
Product Development					
Peter Bohlen.....	2001	215,000	200,000	--	
Senior Vice President	2000	183,750	91,000	--	
Research	1999	170,000	85,000	--	

</Table>

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(1) Amounts shown include compensation deferred pursuant to Section 401(k) of the Code.

(2) Although the Company has no formal bonus plan, the Compensation Committee, in its discretion, may award bonuses to officers and other employees of the Company. The Company has paid bonuses based on individual and Company performance. Certain employment agreements also provide for the payment of minimum guaranteed bonuses. Amounts shown include awards paid relative to services rendered in each of the last three fiscal years. All bonus awards for each of the last three fiscal years were paid in cash. Bonuses are recorded for the period in which they were earned.

(3) Excludes perquisites and other personal benefits for each Named Executive Officer which did not equal or exceed the lesser of $50,000 or 10% of such individual's base salary and bonus for the years ended December 31, 2001, 2000 and 1999, respectively.

(4) Options to purchase the number of shares of common stock shown are recorded for the period in which they were granted.

(5) Pursuant to the terms of the employment agreement entered into between the Company and Dr. Samuel D. Waksal on September 19, 2001, the date the Company entered into its strategic partnership with BMS, Dr. Samuel D. Waksal is guaranteed a minimum annual bonus that is not less than the

difference between $1,000,000 and his base salary for the relevant bonus year. Dr. Samuel D. Waksal's base salary for 2001 was $550,000, and he was paid in 2002 his guaranteed bonus for 2001 of $450,000.

(6) These options were granted pursuant to the terms of each of Dr. Samuel D. Waksal's and Dr. Harlan W. Waksal's employment agreements entered into on September 19, 2001.

(7) Consists of premium payments on a term life insurance policy for Dr. Samuel D. Waksal under which his daughters are the beneficiaries.

(8) Pursuant to the terms of the employment agreement entered into between the Company and Dr. Harlan W. Waksal on September 19, 2001, the date the Company entered into its strategic partnership with BMS, Dr. Harlan W. Waksal is guaranteed a minimum annual bonus that is not less than the difference

between $1,000,000 and his base salary for the relevant bonus year. Dr. Harlan W. Waksal's base salary for 2001 was $455,000, and he was paid in 2002 his guaranteed bonus for 2001 of $545,000.

(9) Mr. Lynch commenced employment with the Company in April 2001.

(10) Consists of a $75,000 sign-on bonus and a performance bonus of $450,000 paid pursuant to the terms of an employment agreement entered into between the Company and Mr. Lynch on September 19, 2001, the date the Company entered into its strategic partnership with BMS.

(11) 200,000 of these options were granted pursuant to the terms of Mr. Lynch's employment agreement entered into on September 19, 2001, the date the Company entered into its strategic partnership with BMS. 60,000 of these options were granted in connection with Mr. Lynch's commencement of employment with the Company.

(12) Options granted on the basis of 2001 performance were granted in 2002 and are not reflected in this Table.

(13) These options were granted to Dr. Tarnowski in connection with his promotion during 2001 to Senior Vice President.

(14) Consists of relocation expenses associated with the individual joining the Company.

OPTION GRANTS IN FISCAL 2001

The following table sets forth certain information relating to stock option grants to the Named Executive Officers during the year ended December 31, 2001.

<Table>
<Caption>

	INDIVIDUAL GRANTS			
	NUMBER OF SECURITIES UNDERLYING OPTIONS	PERCENT OF TOTAL OPTIONS GRANTED TO EMPLOYEES IN	EXERCISE OF BASE PRICE	EXPIRATION

NAME	GRANTED(1)	FISCAL 2001	($/SHARE)(2)	DATE
<S>	<C>	<C>	<C>	<C>
Samuel D. Waksal.....	1,250,000(4)	33.62%	$50.01	9/18/11
Harlan W. Waksal.....	1,000,000(4)	26.90%	50.01	9/18/11
Daniel S. Lynch(5)...	200,000(6)	5.38%	50.01	9/18/11
	60,000(6)	1.61%	28.19	4/2/11
S. Joseph Tarnowski(5).....	10,000(7)	.27%	37.40	5/6/11
Peter Bohlen(5).....	--	--	--	--

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(1) The Company granted options to purchase a total of 3,717,500 shares of common stock to employees during 2001. Grants made to employees relating to 2001 performance were made in 2002.

(2) Options were granted to purchase common stock at an exercise price that equaled the fair market value of the common stock at the time of grant.

(3) The amounts set forth in the three columns represent hypothetical gains that might be achieved by the holders if the respective options are exercised at the end of the their terms. These gains are based on assumed rates of stock price appreciation of 0%, 5% and 10% compounced annually from the dates the respective options were granted.

(4) These options were granted pursuant to the terms of each of Dr. Samuel D. Waksal's and Dr. Harlan W. Waksal's employment agreements entered into on September 19, 2001 and will vest as to 100% of the shares subject thereto on the third anniversary of the date of grant; provided, that, they will automatically vest earlier as to 33 1/3% of the shares subject to the options on the date the Company's ten day average stock price reaches $60, $80 and $100 per share, respectively, should that occur. In addition, the options shall become 100% vested upon a "change in control" of the Company. These options vested as to the first 33 1/3% on October 31, 2001.

(5) Options granted on the basis of 2001 performance were granted in 2002 and are not included in this Table.

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(6) 200,000 of these options were granted pursuant to the terms of Mr. Lynch's employment agreement entered into on September 19, 2001 and are exercisable as to 33 1/3% of the shares on each of the first, second and third anniversaries of the date of grant. 60,000 of these options were granted upon the commencement of Mr. Lynch's employment with the Company and are exercisable as to 25% of the shares on each of the first, second, third and fourth anniversaries of the date of grant.

(7) These options are exercisable as to 25% of the shares on each of the first, second, third and fourth anniversaries of the date of grant.

OPTION EXERCISES AND VALUES FOR FISCAL 2001

The following table sets forth option exercises during the year ended December 31, 2001 by the Named Executive Officers and the value of the options held by such persons on December 31, 2001, whether or not exercisable on such date.

<Table>
<Caption>

NAME	SHARES ACQUIRED ON EXERCISE (#)	VALUE REALIZED(1) ($)	UNDERLYING OPTIONS AT DECEMBER 31, 2001 EXERCISABLE (#)	UNEXERCISABL (#)
<S>	<C>	<C>	<C>	<C>
Samuel D. Waksal	2,300,000	$72,015,350	416,668	833,332
Harlan W. Waksal	2,580,000	89,145,000	333,334	666,666
Daniel S. Lynch	0	0	0	260,000
S. Joseph Tarnowski	19,324	1,002,035	53,676	97,000
Peter Bohlen	46,833	2,589,865	208,667	64,500

</Table>

(1) The values realized were calculated by multiplying the closing market price of the common stock on the date of exercise by the respective number of shares exercised and subtracting the aggregate exercise price. Accordingly, such values realized assume a sale of such common stock on the date of exercise, which in most cases did not occur.

(2) The values were calculated by multiplying the closing market price of the common stock on December 31, 2001 ($46.46 per share as reported by the Nasdaq National Market on that date) by the respective number of shares and subtracting the aggregate exercise price, without making any adjustments for vesting, termination contingencies or other variables. If the exercise price of an option is equal to or greater than $46.46, the option is deemed to have no value.

OTHER BENEFIT PLANS

The Company has no defined benefit or defined contribution retirement plans other than the ImClone Systems Incorporated 401(k) Employee Savings Plan (the "401(k)") established under Section 401(k) of the Code. Contributions to the Plan are voluntary, and substantially all full-time employees are eligible to participate. For 2002, the Company has elected to make voluntary matching contributions equal to 25% of the first 6% of an employee's eligible compensation contributed by the employee, limited to $2,500 per employees. The Company made such a matching contribution for 2001 which totaled approximately $243,000. The Company anticipates evaluating the level of its matching contribution, if any, on an annual basis.

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COMMON STOCK PRICE PERFORMANCE

The graph below provides a comparison of the cumulative total return (assuming reinvestment of dividends) for the Company (which paid no dividends) with The Nasdaq Stock Market (U.S. Companies) Total Return Index and The Nasdaq Pharmaceutical Stocks Total Return Index for the period from December 31, 1996 through December 31, 2001. The graph assumes $100 was invested in the Company's common stock and each of the indexes at the beginning of such period. The Nasdaq Stock Market (U.S. Companies) Total Return Index comprises all domestic common shares traded on the Nasdaq National Market and the Nasdaq SmallCap Market. The Nasdaq Pharmaceutical Stocks Total Return Index represents all companies.

including biotechnology companies, trading on Nasdaq classified under the Standard Industrial Classification Code for pharmaceuticals.

COMPARISON OF FIVE YEAR TOTAL RETURN AMONG IMCLONE COMPANY STOCK, NASDAQ STOCK MARKET (U.S. COMPANIES) TOTAL RETURN INDEX AND NASDAQ PHARMACEUTICAL STOCKS TOTAL RETURN INDEX

[PERFORMANCE GRAPH]

<Table>
<Caption>

		NADSDAQ US	NASDAQ
<S>	<C>		<C>
12/31/96		$ 100.00	$
12/31/97		122.00	
12/31/98		173.00	
12/31/99		321.00	
12/31/00		193.00	
12/31/01		153.00	

</Table>

The material under the caption "Common Stock Price Performance" shall not be deemed to be soliciting material, to be filed with the SEC or to be incorporated by reference into any of the Company's previous or future filings with the SEC, except as otherwise explicitly specified by the Company in any such filing.

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CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS

RELATIONSHIP WITH BRISTOL-MYERS SQUIBB COMPANY

Two of the Company's Directors, Dr. Andrew G. Bodnar and Dr. Peter S. Ringrose, are also officers of BMS. The Company's relationship with BMS is described below.

On September 19, 2001, the Company entered into an acquisition agreement (the "Acquisition Agreement") with BMS, a Delaware corporation, and Bristol-Myers Squibb Biologics Company, a Delaware corporation ("BMS Biologics"), which is a wholly-owned subsidiary of BMS, providing for the tender offer by BMS Biologics to purchase up to 14,392,003 shares of the Company's common stock for $70.00 per share, net to the seller in cash. The tender offer by BMS Biologics, available to all stockholders, allowed for the Company's present or former employees and Directors who held exercisable options to purchase shares of the Company's common stock having exercise prices less than $70.00 per share to conditionally exercise any or all of those options and tender the underlying shares in the tender offer. In connection with the Acquisition Agreement, the Company entered into a stockholder agreement with BMS and BMS Biologics, dated as of September 19, 2001 (the "Stockholder Agreement"), pursuant to which the Company agreed with BMS and BMS Biologics to various arrangements regarding the respective rights and obligations of each party with respect to, among other things, the ownership of shares of the Company's common stock by BMS and BMS Biologics. Concurrently with the execution of the

Acquisition Agreement and the Stockholder Agreement, the Company entered into a development, promotion, distribution and supply agreement (the "Commercial Agreement") with BMS and E.R. Squibb & Sons, L.L.C., a Delaware limited liability company and a wholly-owned subsidiary of BMS ("E.R. Squibb"), relating to ERBITUX, the Company's lead therapeutic product, pursuant to which, among other things, the parties are co-developing and co-promoting ERBITUX in the United States and Canada, and co-developing ERBITUX (together with Merck KGaA) in Japan.

On March 5, 2002, the Company amended the Commercial Agreement with E.R. Squibb and BMS. The amendment changed certain economics of the Commercial Agreement and has expanded the clinical and strategic role of BMS in the ERBITUX development program. One of the principal economic changes to the Commercial Agreement is that the Company received $140,000,000 on March 7, 2002, and an additional payment of $60,000,000 is payable on March 5, 2003. Such payments are in lieu of the $300,000,000 payment the Company would have received on acceptance by the United States Food and Drug Administration ("FDA") of the ERBITUX Biologics License Application under the original terms of the Commercial Agreement. In addition, the Company agreed to resume construction of its second commercial manufacturing facility as soon as reasonably practicable after the execution of the amendment.

On October 29, 2001, pursuant to the Acquisition Agreement, BMS Biologics accepted for payment pursuant to the tender offer 14,392,003 shares the Company's common stock on a pro rata basis from all tendering shareholders and those conditionally exercising stock options.

The Stockholder Agreement, among other things, gave BMS the right to nominate two initial directors and also set forth BMS' (i) limitation on additional purchases of shares, (ii) option to purchase shares in the event of dilution and (iii) restrictions as to transfer of shares. Currently, BMS has designated Dr. Ringrose, BMS's Chief Scientific Officer, and Dr. Bodnar, BMS's Senior Vice President, Medical and External Affairs, as the initial BMS directors.

In exchange for the rights granted to BMS under the amended Commercial Agreement, the Company can receive up-front and milestone payments totaling $900,000,000 in the aggregate, of which $200,000,000 was received on September 19, 2001, $140,000,000 was received on March 7, 2002, $60,000,000 is payable on March 5, 2003, $250,000,000 is payable upon receipt of marketing approval from the FDA with

respect to the initial indication for ERBITUX and $250,000,000 is payable upon receipt of marketing approval from the FDA with respect to a second indication for ERBITUX. All such payments are non-refundable and non-creditable. Except for the Company's expenses incurred pursuant to a co-promotion option, E.R. Squibb is also responsible for 100% of the distribution, sales and marketing costs in the United States and Canada, and as between the Company and E.R. Squibb, each will be responsible for 50% of the distribution, sales, marketing costs and other related costs and expenses in Japan. The Commercial Agreement provides that E.R. Squibb shall pay the Company distribution fees based on a percentage of annual net sales of ERBITUX by E.R. Squibb in the United States and Canada. The distribution fee is 39% of net sales in the United States and Canada. The Commercial Agreement also provides that the distribution fees for the sale of ERBITUX in Japan by E.R. Squibb or the Company shall be equal to 50% of operating profit or loss with respect to such sales for any calendar month. In the event of an operating profit, E.R. Squibb will pay the Company the amount of

such distribution fee, and in the event of an operating loss, the Company will credit E.R. Squibb the amount of such distribution fee. The Commercial Agreement provides that the Company will be responsible for the manufacture and supply of all requirements of ERBITUX in bulk form for clinical and commercial use in the United States, Canada and Japan and that E.R. Squibb will purchase all of its requirements of ERBITUX in bulk form for commercial use from the Company. The Company will supply ERBITUX in bulk form for clinical use at the Company's fully burdened manufacturing cost and will supply ERBITUX in bulk form for commercial use at our fully burdened manufacturing cost plus a mark-up of 10%. In addition to the up-front and milestone payments, the distribution fees for the United States, Canada and Japan and the 10% mark-up on the commercial supply of ERBITUX, E.R. Squibb is also responsible for 100% of the cost of all clinical studies other than those studies undertaken post-launch which are not pursuant to an Investigational New Drug Application (e.g. phase IV studies), the cost of which will be shared equally between E.R. Squibb and the Company. As between E.R. Squibb and the Company, each will be responsible for 50% of the cost of all clinical studies in Japan.

OTHER ITEMS

The Company accepted from Dr. Samuel D. Waksal, its President and Chief Executive Officer, a full recourse, unsecured promissory note dated as of December 21, 2000 in the principal amount of $282,200. The note was payable upon the earlier of June 21, 2001 or demand by the Company and bore interest at 10.5% (the prime lending rate plus 1% on the date of the note) for the period that the loan is outstanding. The Company extended the term of the note to December 21, 2001. As of November 14, 2001, the principal amount of this note and accrued interest totaling $310,000 had been paid in full.

In July 2001, the Company accepted a promissory note from each of Dr. Samuel D. Waksal, its President and Chief Executive Officer, Dr. Harlan W. Waksal, its Executive Vice President and Chief Operating Officer and Mr. Robert F. Goldhammer, its Chairman of the Board, and, in August 2001, the Company accepted a promissory note from Dr. Arnold J. Levine, a member of its Board of Directors, in payment of the aggregate exercise price associated with the exercise of stock options and warrants they held to purchase a total of approximately 4,473,000 shares of the Company's common stock. Dr. Samuel D. Waksal's promissory note was in the amount of $18,178,750; Dr. Harlan W. Waksal's promissory note was in the amount of $15,747,550; Mr. Goldhammer's promissory note was in the amount of $1,228,065; and Dr. Levine's promissory note was in the amount of $87,000. The unsecured promissory notes were full-recourse, payable on the earlier of one year from the date of the notes or on demand by the Company and bore interest at the prime lending rate plus 1% (7 3/4% on the date of the note). Interest was payable quarterly and the interest rate adjusted quarterly during the term of each note to the then current prime lending rate plus 1%. On October 31, 2001, the Company made demand for repayment by November 23, 2001, of the principal amount of the notes and accrued interest thereon. As of November 14, 2001, the principal amount of all of these notes of $35,241,000 and accrued interest of $879,000 were paid in full.

In December 2001, the Company entered into an agreement to sublease a 1,520 square foot portion of its corporate headquarters and research facility in New York City to Scientia Health Group Inc. ("Scientia"). Base rent under the sublease is $5,496 per month and is subject to annual escalation. Scientia is also responsible for additional rent representing its pro-rata share of operating expenses. The amount charged

to Scientia represents a direct pass through of the Company's costs. The term of the sublease shall continue month to month until such notice of termination by the Company. During the year ended December 31, 2001, the Company incurred, and was subsequently reimbursed by Scientia, for approximately $111,000 in costs associated with preparing the premises for occupancy. Dr. Samuel D. Waksal, the Company's President and Chief Executive Officer, is the Executive Chairman of Scientia.

Certain transactions engaged in by Dr. Samuel D. Waksal, the Company's President and Chief Executive Officer, in securities of the Company were deemed to have resulted in "short-swing profits" under Section 16 of the Exchange Act. In accordance with Section 16(b) of the Exchange Act, Dr. Samuel D. Waksal paid the Company in March 2002 an aggregate amount of approximately $486,000, as disgorgement of "short-swing profits" he realized.

During the year ended December 31, 2001, the Company paid Dr. Vincent T. DeVita, Jr., a Director of the Company, a total of $100,000 for scientific consulting services provided to the Company by Dr. DeVita, which services have been terminated.

SECTION 16(a) BENEFICIAL OWNERSHIP REPORTING COMPLIANCE

Section 16(a) of the Securities Exchange Act requires the Company's officers and directors, and persons who own more than ten percent of a registered class of the Company's equity securities, to file with the SEC reports of ownership of Company securities and changes in reported ownership. Officers, directors and greater than ten percent shareholders are required by SEC rules to furnish the Company with copies of all Section 16(a) reports they file.

Based solely on a review of the copies of such forms furnished to the Company, or written representations from the reporting persons that no Form 5 was required, the Company believes that, during the fiscal year ended December 31, 2001, all Section 16(a) filing requirements applicable to its officers, directors, and greater than ten percent beneficial owners were met, except that, between 1992 and 2001, Dr. Samuel D. Waksal failed to timely file 17 Forms 4 with respect to 26 transactions and 6 Forms 5 with respect to 17 transactions. In addition, Dr. Harlan W. Waksal failed to timely report ownership of 200 shares owned jointly with his wife and failed to include 43 of such shares as part of a sale timely reported on a Form 4. Information concerning these shares and the transaction was promptly reported to the SEC upon discovery of the omissions.

REPORT OF THE AUDIT COMMITTEE

MEMBERSHIP AND ROLE OF THE AUDIT COMMITTEE

The Audit Committee consists of the following members of the Company's Board of Directors: Paul B. Kopperl, Chairman, and William R. Miller. During 2001, Richard Barth and Andrew G. Bodnar served on the Audit Committee. Dr. Bodnar resigned from the Audit Committee on March 4, 2002, and Mr. Barth resigned from the Board of Directors on April 2, 2002. Mr. Barth was a member of the Audit Committee on March 22, 2002, the date this Report was adopted. The Board of Directors, in its business judgment, has determined that each of the members of the Audit Committee is "independent" as defined under the National Association of Securities Dealers' listing standards. The Audit Committee operates under a written charter adopted by the Board of Directors on June 14, 2000, a copy of which was included as Appendix A to the Company's proxy statement for the 2000 fiscal year. On November 15, 2001, the Audit Committee

reviewed and reassessed the adequacy of the charter and the performance of the Audit Committee thereunder. The Audit Committee held three (3) meetings during the fiscal year ended December 31, 2001.

The primary functions of the Audit Committee are to monitor the integrity of the Company's financial reporting process and systems of internal controls regarding finance, accounting and, with certain exceptions, legal compliance and to provide an avenue of communication among the independent auditors, management and the Board of Directors. In performing all of these functions, the Audit Committee acts only in an oversight capacity on behalf of the Board of Directors. The primary duties and responsibilities of the

Audit Committee are to (i) review the Company's annual audited financial statements prior to filing with the SEC or distribution to the public; (ii) in consultation with management and the independent auditors, consider the integrity of the Company's financial reporting procedures and controls; (iii) review with management and the independent auditors the Company's quarterly financial statements prior to filing with the SEC or distribution to the public; (iv) periodically perform self-assessment of Audit Committee performance; (v) annually review policies and procedures as well as test results associated with directors' and officers' expense accounts and perquisites; and (vi) annually review a summary of directors' and officers' related party transactions and potential conflicts of interest. The Audit Committee also reviews the performance of the independent auditors and their fees and recommends their selection and engagement to the Board of Directors.

REVIEW OF THE COMPANY'S AUDITED FINANCIAL STATEMENTS FOR THE FISCAL YEAR ENDED DECEMBER 31, 2001

The Audit Committee reviewed and discussed the audited financial statements of the Company for the fiscal year ended December 31, 2001 with the Company's management and KPMG LLP, the Company's auditors. This discussion included an assessment of the quality, not just the acceptability, of the accounting principles, the reasonableness of significant estimates and judgments and the clarity of disclosures in the financial statements. In addressing the quality of management's accounting judgments, the members of the Audit Committee asked for management's representations that the audited financial statements of the Company have been prepared in conformity with accounting principles generally accepted in the United States of America and have expressed their general preference for conservative policies when more than one accounting option is available.

The Audit Committee also discussed with its independent auditors the matters required to be discussed by Statement on Auditing Standards No. 61 (Communication with Audit Committees), as currently in effect, and, with and without management present, reviewed and discussed the results of the independent auditors' examination of the financial statements.

Consistent with Independence Standards Board Standard No. 1 (Independence Discussion with Audit Committees), as currently in effect, the Audit Committee obtained from KPMG LLP a formal written statement describing all relationships between the auditors and the Company that might bear on the auditors' independence from the Company and its management. The Audit Committee discussed with management and with the auditors the provision of non-audit services and any relationships that may impact the auditors' objectivity and independence and has satisfied itself as to the auditors' independence.

In performing all of these functions, the Audit Committee acts only in

an oversight capacity on behalf of the Board of Directors. In its oversight role, the Audit Committee necessarily relies on the procedures, work and assurances of the Company's management, which has the primary responsibility for financial statements and reports, and of the independent auditors, who, in their report, express an opinion on the conformity of the Company's audited financial statements to accounting principles generally accepted in the United States of America.

Based on the Audit Committee's review and discussions noted above, the Audit Committee recommended to the Board of Directors that the Company's audited financial statements be included in the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2001.

The Audit Committee and Board of Directors have recommended, subject to ratification by the stockholders, that KPMG LLP be selected as the Company's independent certified public accountants for the fiscal year ending December 31, 2002.

Audit Committee

Paul B. Kopperl, Chairman
Richard Barth
William R. Miller

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The foregoing Report of the Audit Committee shall not be deemed to be soliciting material, to be filed with the SEC or to be incorporated by reference into any of the Company's previous or future filings with the SEC, except as otherwise explicitly specified by the Company in any such filing.

FEES PAID TO KPMG LLP

AUDIT FEES

The aggregate fees billed by KPMG LLP in connection with its audit of the Company's annual financial statements for the year 2001 and its review of the financial statements included in the Company's Form 10-Qs during 2001 were $174,000.

FINANCIAL INFORMATION SYSTEMS DESIGN AND IMPLEMENTATION FEES

The Company did not engage KPMG LLP to provide services for the Company regarding financial information systems design and implementation during 2001.

ALL OTHER FEES

KPMG LLP's fees for all other professional services provided to the Company during 2001 totaled $240,000, including audit related services of $96,000 and non-audit related services of $144,000. Audit related services included fees related to the review of SEC registration statements and various technical accounting consultations. Non-audit related services consisted primarily of fees related to tax services, including services rendered in connection with the BMS transaction. The Audit Committee has considered whether the provision of all other services by KPMG LLP is compatible with maintaining KPMG LLP's independence and concluded that KPMG LLP is "independent."

PROPOSAL NO. 2

APPROVAL OF THE IMCLONE SYSTEMS INCORPORATED

2002 STOCK OPTION PLAN

On April 3, 2002, the Board of Directors adopted, subject to stockholder approval, the ImClone Systems Incorporated 2002 Stock Option Plan for the purpose of enhancing the ability of the Company and its subsidiaries to attract and retain officers, employees, directors and consultants of outstanding ability and to provide officers, employees, directors and consultants with an interest in the Company parallel to that of the Company's stockholders. The Compensation Committee has determined that the Company's current Chief Executive Officer and Chief Operating Officer will not receive option grants under the 2002 Stock Option Plan during 2002. For the period of 2003 and beyond, the Compensation Committee will assess the appropriateness of granting options to such individuals based upon their performance and the principles of sound corporate governance. A brief description of the major provisions of the plan is set forth below to facilitate an informed decision by the shareholders entitled to vote on the approval of the plan. This summary highlights only selected information from the plan and does not contain all of the information that may be important to you. To understand the terms of the plan fully, you should read the full text of the plan, a copy of which is attached hereto as Appendix A. The affirmative vote of a majority of the outstanding shares present and entitled to vote at the annual meeting is required to approve the plan.

Administration. The plan shall be administered by a committee (the "Committee") which shall consist of at least two members of the Board of Directors who are "non-employee directors" within the meaning of Rule 16b-3 as promulgated under Section 16 of the Securities Exchange Act of 1934, as amended and who are also "outside directors" within the meaning of Section 162(m) of the Internal Revenue Code. The Committee will have broad discretion, subject to the terms of the plan, to approve the selection of participants, prescribe the terms and conditions of options and establish rules and regulations for the interpretation and administration of the plan.

In order to administer the plan in an efficient manner, the Committee may delegate to officers or employees of the Company or any subsidiary, and to service providers, the authority, subject to such terms as the Committee shall determine, to perform administrative functions with respect to the plan and option awards.

Under the plan, members of the Committee shall not be personally liable for any actions taken in good faith with respect to the plan and shall, to the extent permitted by law, be fully indemnified by the Company with respect to any such action or determination.

Eligibility. Individuals eligible to receive options under the plan shall be the officers, employees, directors and consultants of the Company and its subsidiaries selected by the Committee; provided that, only employees of the Company and its subsidiaries may be granted incentive stock options.

Stock Subject to the Plan. Common stock available for issue or distribution under the plan shall be authorized and unissued shares or shares reacquired by the Company in any manner. Subject to adjustment under the plan, the maximum total number of shares of common stock which shall be available for the grant of options under the plan shall be 3,300,000. For purposes of this limitation, any common stock subject to an option which is canceled, forfeited or expires prior to exercise whether such option was granted under this plan or the 1998 Non-Qualified Stock Option Plan, as amended, the 1996 Non-Qualified Stock Option Plan, as amended or the 1996 Incentive Stock Option Plan, as

amended (together the "Prior Plans") shall again become available for grant under the plan. In addition, any shares of common stock tendered and/or withheld for payment of all or a portion of an option or any applicable withholding taxes shall again become available for the grant of an option under the plan. The Company may, but is not required to, use the proceeds it receives in connection with the exercise of an option under this plan or under the Prior Plans for exercises occurring after the "Effective Date" (i.e., the date the plan is approved by a majority vote of the Company's shares present and entitled to vote at the annual meeting) to purchase shares of its common stock in the open market and any such shares may be used for the issuance of options under this plan. Subject to adjustment under the plan, no employee shall be granted, during any three (3) year period, options to purchase more than 3,300,000 shares of common stock.

Subject to adjustment under the plan, the aggregate number of shares of common stock with respect to which incentive stock options may be granted under the plan shall not exceed 825,000 shares of common stock. Any shares of common stock subject to an incentive stock option granted under the plan or the 1996 Incentive Stock Option Plan, as amended which is canceled, forfeited or expires prior to exercise shall again be counted toward the aggregate number of shares available for the grant of incentive stock options under this plan.

If the stockholders approve this plan, no further grants will be made under the Prior Plans.

The market value of the Company's common stock as reported on Nasdaq as of April 22, 2002 was $19.97 per share.

Nothing in the plan prohibits the Company from adopting other equity compensation programs for employees of the Company and its subsidiaries, including employees eligible for grants under the plan.

Type of Awards. Incentive stock options and nonqualified stock options may be granted under the plan.

Purchase Price. The purchase price per share of common stock purchasable under an option shall be determined by the Committee and shall not be less than 100% of the fair market value of the common stock on the date of grant.

Option Term. Unless otherwise provided at the time of grant, the term of each option shall be ten (10) years from the date the option is granted. Unless otherwise provided at the time of grant, upon the death or disability of a participant, options (other than incentive stock options) that would otherwise remain exercisable following such death or disability shall remain exercisable for one year following such death or disability, notwithstanding the term of the option.

Exercisability; Method of Exercise. Each option shall vest and become exercisable at a rate determined by the Committee on the date of grant.

Options may be exercised, in whole or in part, by written notice to the Company, specifying the number of shares to be purchased together with payment in full of the exercise price. The exercise price may be paid by (i) cash or certified check or bank check, (ii) surrender of common stock held by the optionee for at least six (6) months (or such longer or shorter period as may be required to avoid a charge to earnings for accounting purposes) or the

attestation of ownership of such shares, in either case, if so permitted by the Company, (iii) through a broker-assisted same-day sale, (iv) through additional methods prescribed by the Committee or (v) by any combination of the foregoing, to the extent permitted by applicable law.

Termination of Continuous Service. Unless otherwise provided at the time of grant, upon a termination of continuous service by an optionee, all unvested options shall terminate and all vested options shall remain exercisable for 30 days thereafter (one year in the event of death or disability); provided, that, if such termination is for cause, all options (whether or not vested) shall terminate and cease to be exercisable.

Withholding Tax. The Company has the right to require any optionee to pay to the Company any amount of taxes which the Company shall be required to withhold with respect to the exercise of an option. Such obligation may be satisfied as follows (i) in cash or (ii) with the consent of the Committee and in its sole discretion, the participant may elect to have the Company withhold shares of common stock having a fair market value equal to the amount of the withholding tax obligation as determined by the Company.

Acceleration of Exercisability. Unless otherwise provided at the time of grant, upon the occurrence of a Change in Control (as defined in the plan), all options shall automatically become vested and exercisable in full.

Forfeiture. Unless otherwise provided at the time of grant, in the event of a serious breach of conduct by a participant or former participant, the Committee may (i) cancel any outstanding option granted to such participant or former participant, in whole or in part, whether or not vested, and/or (ii) if such conduct or activity occurs within one (1) year following the exercise of an option, require such participant or former participant to repay to the Company any gain realized upon the exercise of such option.

Adjustments. The Committee will determine the appropriate adjustments to be made in order to prevent dilution or enlargement of the benefits or potential benefits intended to be made available under the plan or with respect to an option upon the occurrence of certain events affecting the capitalization of the Company.

Termination and Amendment of the Plan. Subject to earlier termination pursuant to the terms of the plan, the plan shall have an indefinite term; provided that, the ability to grant incentive stock options will terminate on April 3, 2012. The Board may amend, suspend or terminate the plan at any time; provided, that, (a) no such amendment shall be made without shareholder approval if such approval is necessary to comply with applicable law, regulation or stock exchange rule and (b) except as provided in the plan, no amendment shall be made that would adversely affect rights previously granted under the plan.

GENERAL FEDERAL TAX CONSEQUENCES

The following summary of the material federal income tax consequences to the Company is based on current law, is for general information only and is not tax advice.

Section 162(m) Limitation. Subject to a limited number of exceptions, Section 162(m) denies a deduction to a publicly held corporation for payments of remuneration to certain employees to the extent the employee's remuneration for the taxable year exceeds $1,000,000. For this purpose, remuneration attributable to stock options is included within the $1,000,000 limitation. However, to the extent that certain procedural requirements are met (e.g., the plan is approved by the stockholders of the Company, grants are made by the Committee, the

exercise price is equal to the fair market value of the underlying shares upon grant, etc.), gain from the exercise of stock options should not be subject to the $1,000,000 limitation.

The Company has attempted to structure the plan in such a manner that the remuneration attributable to the stock options will not be subject to the $1,000,000 limitation. The Company has not, however, requested a ruling from the Internal Revenue Service or an opinion of counsel regarding this issue.

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Non-Qualified Stock Options. An individual receiving non-qualified stock options should not recognize taxable income at the time of grant. A participant should generally recognize ordinary compensation income in an amount equal to the excess, if any, in the fair market value of the option shares on exercise of the non-qualified stock options over the exercise price thereof. In general, subject to the limitations set forth in Section 162(m) and discussed above, the Company is entitled to deduct from its taxable income the amount that the participant is required to include in ordinary income at the time of such inclusion.

Incentive Stock Options. An individual granted an incentive stock option will not generally recognize taxable income at the time of grant or, subject to certain conditions, at the time of exercise, although he or she may be subject to alternative minimum tax. In general, if a disqualifying disposition should occur (i.e., the shares acquired upon exercise of the option are disposed of within the later of two years from the date of grant or one year from the date of exercise), a participant will generally recognize ordinary compensation income in the year of disposition in an amount equal to the excess, if any, of the fair market value of the option shares at the time of exercise (or, if less, the amount realized on disposition), over the exercise price thereof. The Company is not entitled to any deduction on account of the grant of the incentive stock options or the participant's exercise of the option to acquire common stock. However, in the event of a subsequent disqualifying disposition of such shares of common stock acquired pursuant to the exercise of an incentive stock option under circumstances resulting in taxable compensation to the participant, subject to the limitations set forth in Section 162(m) and discussed above, in general, the Company should be entitled to a tax deduction equal to the amount treated as taxable compensation to the participant.

REGISTRATION WITH THE SEC

If this Proposal No. 2 is adopted, the Company intends to file a registration statement covering the offering of the shares under the plan with the SEC pursuant to the Securities Act of 1933, as amended.

NEW PLAN BENEFITS

Because future participation in the plan and the level of participation will vary, it is not possible to determine the value of benefits which may be obtained by those eligible to participate in the plan.

THE BOARD RECOMMENDS A VOTE "FOR" THE APPROVAL OF THE IMCLONE SYSTEMS INCORPORATED 2002 STOCK OPTION PLAN (PROPOSAL NO. 2 ON YOUR PROXY CARD).

PROPOSAL NO. 3

APPROVAL OF AN AMENDMENT TO THE COMPANY'S CERTIFICATE OF INCORPORATION TO INCREASE THE NUMBER OF AUTHORIZED SHARES OF COMMON STOCK

On April 3, 2002, the Board of Directors voted unanimously to submit for stockholder approval a proposed amendment to the Company's Certificate of Incorporation, as amended, to increase the number of authorized shares of common stock from 120,000,000 to 200,000,000 shares. The Board of Directors has declared the proposed amendment to be advisable and in the best interests of the Company and its stockholders and recommends that the stockholders approve the amendment.

As of March 15, 2002, there were approximately:

- 73,333,889 shares of common stock issued and outstanding.

- 12,635,521 shares of common stock reserved for issued and outstanding options, including those issued under the Company's various option plans.

- 2,117,431 additional shares of common stock reserved for issuance under the Company's various option plans.

- 189,250 shares of treasury stock.

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- 948,175 shares of common stock reserved for issuance under the Company's 1998 Employee Stock Purchase Plan, as amended.

- 869,565 shares of common stock reserved for issuance as shares of common stock that may be issued in the event the Company achieves certain milestones in the development of ERBITUX, the Company's lead therapeutic product candidate, pursuant to the terms of a Development and License Agreement entered into with Merck KGaA in December 1998. Under this agreement, Merck KGaA is paying to the Company, among other things, $30 million, assuming the Company achieves certain milestones for which Merck KGaA will receive equity (the "Milestone Shares"), of which $5,000,000 has been received to date and 63,027 shares of common stock issued. These shares will be priced at varying premiums to the then market price of the common stock depending upon the timing of the achievement of the respective milestones. Because the exact number of shares needed to be reserved cannot be determined due to the fluctuating market price and the undetermined premium, the Company has currently reserved a number of shares based upon recent market prices. The 869,565 number set forth above has been calculated based upon the March 15, 2002 closing price. A different number of shares could be required based on fluctuations in the price of the common stock.

- 4,356,508 shares of common stock reserved for issuance upon conversion of the Company's $240 million of 5 1/2% convertible subordinated notes due March 1, 2005, which were privately placed in February 2000. The Company received net proceeds from this offering of approximately $232.2 million, after deducting expenses associated with the offering. A holder may convert all or a portion of a note into common stock at any time on or before March 1, 2005 at a conversion price of $55.09 per share, subject to adjustment if certain events affecting the Company's common stock occur.

- On February 15, 2002, the Board of Directors approved a Stockholder Rights Plan and declared a dividend of one preferred share purchase right (a "Right") for each share of common stock outstanding at the

close of business on February 19, 2002. Under certain conditions, each right entitles the holder thereof to purchase from the Company one one-hundredth of a share of Series B Participating Cumulative Preferred Stock, par value $0.001 per share (the "Preferred Stock"), of the Company at an exercise price of $175 per one one-hundredth of a share of Preferred Stock. Subject to certain exceptions, the Rights become exercisable if a person or group acquires 15% or more of the Company's common stock. If the Rights become exercisable, each holder of a Right with the exception of the 15% holder, would be entitled to buy additional shares of the Company's common stock at half of the then current market price. The Board of Directors may redeem all of the Rights at a price of $0.001 per Right at any time before any person or group has acquired 15% of the Company's stock without meeting one of the exceptions. No shares of common stock were reserved for issuance in connection with this plan.

Accordingly, giving effect to such issuances and reserves, approximately 25,549,661 shares of common stock of the 120,000,000 currently authorized would remain available for issuance. If Proposal No. 2 described in this proxy statement is approved by stockholders at the meeting, approximately 24,367,092 shares of common stock would be available for issuance unless this Proposal No. 3 is approved.

The Company has no present agreement, commitment, plan or intent to issue any of the additional shares of common stock provided for in this Proposal other than as discussed herein. If this Proposal is approved, the additional authorized common stock, as well as the currently authorized but unissued common stock (but for those shares which are reserved), would be immediately available in the future for such corporate purposes as the Board deems advisable from time to time without further action by the stockholders, unless such action is required by applicable law or any stock exchange or securities market upon which the Company's shares may be listed.

The additional authorized common stock resulting from the approval of this Proposal will have the same terms and rights as the existing common stock. Holders of the common stock of the Company do not presently have preemptive rights nor will they as a result of the approval of this Proposal.

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The Board anticipates that the authorized common stock in excess of those shares issued and reserved for issuance (including, if authorized, the additional common stock provided for in this Proposal) will be utilized for general corporate purposes, including grants of stock options. These shares may also be publicly sold or privately placed as part of financing transactions and may be used by the Company in connection with acquisitions, commercial agreements and stock splits. Such an increase in shares also could be used to make a change in control of the Company more difficult. Although the Company has no current plan or intention to issue such shares as a takeover defense, the additional authorized shares could be used to discourage persons from attempting to gain control of the Company or to make the removal of management more difficult. Management is not currently aware of any specific effort to obtain control of the Company by means of a merger, tender offer, solicitation in opposition to management, or otherwise. Management may itself from time to time consider a number of strategic alternatives designed to increase shareholder value, including joint ventures, acquisitions and other forms of alliances as well as the sale of all or part of the Company, and may determine to issue shares in connection with such a transaction.

It should be noted that, subject to the limitations discussed above, the

Board can currently take all of the types of Board action described in the preceding paragraphs. The power of the Board to take such actions would not be enhanced by the passage of this Proposal, although this Proposal would increase the number of shares of common stock that are subject to such action. Under Delaware law, stockholders will not have any dissenters' or appraisal rights in connection with this amendment. If the stockholders approve the amendment, it will become effective upon the Company's executing, acknowledging and filing a Certificate of Amendment with the Secretary of State of Delaware.

AN AFFIRMATIVE VOTE OF A MAJORITY OF SHARES OF COMMON STOCK OUTSTANDING AND ENTITLED TO VOTE ON THE PROPOSAL WILL CONSTITUTE APPROVAL.

If this Proposal is approved and the amendment to the Certificate of Incorporation becomes effective, the first paragraph of Article FOURTH of the Certificate of Incorporation, which sets forth the Company's presently authorized capital stock, will be amended to read as follows:

> "FOURTH: The total number of shares of capital stock which the Corporation shall have the authority to issue is two hundred million (200,000,000) shares of common stock with a par value of one tenth of one cent ($.001) per share and four million (4,000,000) shares of preferred stock with a par value of one dollar ($1.00) per share."

THE BOARD RECOMMENDS A VOTE "FOR" APPROVAL OF THE AMENDMENT TO THE COMPANY'S CERTIFICATE OF INCORPORATION TO INCREASE THE TOTAL NUMBER OF AUTHORIZED SHARES OF COMMON STOCK FROM 120,000,000 TO 200,000,000 (PROPOSAL NO. 3 ON YOUR PROXY CARD).

PROPOSAL NO. 4

RATIFICATION OF INDEPENDENT CERTIFIED PUBLIC ACCOUNTANTS

The Audit Committee and the Board have selected KPMG LLP as the Company's independent certified public accountants for the year ending December 31, 2002. KPMG LLP has served as the Company's auditor since 1980. The ratification of the selection of independent certified public accountants is to be voted upon at the meeting, and it is intended that the persons named in the accompanying proxy will vote for KPMG LLP. Representatives of KPMG LLP are expected to attend the meeting, to have an opportunity to make a statement if they desire to do so and to be available to respond to appropriate questions.

THE BOARD RECOMMENDS A VOTE "FOR" THE RATIFICATION OF THE SELECTION OF KPMG LLP TO ACT AS THE COMPANY'S INDEPENDENT CERTIFIED PUBLIC ACCOUNTANTS FOR THE YEAR ENDING DECEMBER 31, 2002 (PROPOSAL NO. 4 ON YOUR PROXY CARD).

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STOCKHOLDER PROPOSALS

A stockholder proposal intended to be presented at the Company's Annual Meeting of Stockholders to be held in 2003 must be received by the Company on or before January 23, 2003 in order to be included in the Company's proxy statement and form of proxy relating to that meeting. In addition, the Company's By-laws provide that any stockholder wishing to present a proposal or to nominate a candidate for Director at an annual meeting must give notice to the Secretary of the Company not less than 60 nor more than 90 days prior to the date of the meeting. If, however, the date of the meeting is first publicly announced or disclosed (in a public filing or otherwise) less than 70 days prior to the date of the meeting, such advance notice shall be given not more than ten days after

such date is first announced or disclosed. You may obtain a copy of the Company's By-laws by writing to the Secretary of the Company at the address shown on the cover of this proxy statement.

OTHER MATTERS

The Board of Directors does not know of any matters, other than those referred to in this proxy statement, to be presented at the meeting for action by the stockholders. However, if any other matters are properly brought before the meeting or any postponements or adjournments thereof, it is intended that votes will be cast with respect to such matters, pursuant to the proxies, in accordance with the recommendations of the Board of Directors or, if no recommendation is given, in the discretion of the person acting under the proxies.

By Order of the Board of Directors

/s/ Daniel S. Lynch

Daniel S. Lynch
Secretary

New York, New York
April 29, 2002

IT IS IMPORTANT THAT PROXIES BE RETURNED PROMPTLY. NO MATTER HOW LARGE OR SMALL YOUR HOLDINGS MAY BE, WE URGE YOU TO FILL IN, SIGN AND RETURN THE ACCOMPANYING PROXY CARD OR FOLLOW THE PROCEDURES OUTLINED ON THE PROXY CARD TO VOTE BY TELEPHONE OR VIA THE INTERNET.

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APPENDIX A

IMCLONE SYSTEMS INCORPORATED
2002 STOCK OPTION PLAN

1. Purpose. The purpose of the ImClone Systems Incorporated 2002 Stock Option Plan (the "Plan") is to enhance the ability of ImClone Systems Incorporated (the "Company") and its Subsidiaries to attract and retain officers, employees, directors and consultants of outstanding ability and to provide officers, employees, directors and consultants with an interest in the Company parallel to that of the Company's shareholders. The term "Company" as used in this Plan with reference to employment or service shall include the Company and its Subsidiaries, as appropriate.

2. Definitions.

(a) "Board" shall mean the Board of Directors of the Company.

(b) "Cause" shall mean (i) if a Participant is party to an employment agreement or similar agreement with the Company and such agreement includes a definition of Cause, the definition contained therein or (ii) if no such employment or similar agreement exists, it shall mean (A) the Participant's failure to substantially perform the duties reasonably assigned to him or her by the Company, which has not been cured by the Participant following 10 days prior written notice from the Company, (B) a good faith finding by the Company of the Participant's dishonesty, gross negligence or misconduct, (C) a material breach by the Participant of any written Company employment policies or rules or (D)

the Participant's conviction for, or his or her plea of guilty or nolo contendere to, a felony or for any other crime which involves fraud, dishonesty or moral turpitude.

(c) "Change in Control" of the Company means the occurrence of one of the following events:

(i) individuals who, on the Effective Date, constitute the Board (the "Incumbent Directors") cease for any reason to constitute at least a majority of the Board, provided that any person becoming a director subsequent to the Effective Date whose election or nomination for election was approved by a vote of at least two-thirds of the Incumbent Directors then on the Board (either by a specific vote or by approval of the proxy statement of the Company in which such person is named as a nominee for director, without objection to such nomination) shall be an Incumbent Director; provided, however, that no individual initially elected or nominated as a director of the Company as a result of an actual or threatened election contest with respect to directors or as a result of any other actual or threatened solicitation of proxies by or on behalf of any person other than the Board shall be an Incumbent Director;

(ii) any "person" (as such term is defined in Section 3(a)(9) of the Securities Exchange Act of 1934 (the "Exchange Act") and as used in Sections 13(d)(3) and 14(d)(2) of the Exchange Act) is or becomes, after the Effective Date, a "beneficial owner" (as defined in Rule 13d-3 under the Exchange Act), directly or indirectly, of securities of the Company representing 35% or more of the combined voting power of the Company's then outstanding securities eligible to vote for the election of the Board (the "Company Voting Securities"); provided, however, that an event described in this paragraph (ii) shall not be deemed to be a Change in Control if any of following becomes such a beneficial owner: (A) the Company or any majority-owned subsidiary (provided, that this exclusion applies solely to the ownership levels of the Company or the majority-owned subsidiary), (B) any tax-qualified, broad-based employee benefit plan sponsored or maintained by the Company or any majority-owned subsidiary, (C) any underwriter temporarily holding securities pursuant to an offering of such securities, or (D) any person pursuant to a Non-Qualifying Transaction (as defined in paragraph (iii));

(iii) the consummation of a merger, consolidation, statutory share exchange or similar form of corporate transaction involving the Company or any of its Subsidiaries that requires the approval of the Company's stockholders, whether for such transaction or the issuance of securities in the transaction (a "Business Combination"), unless immediately following such Business Combination: (A) 60% or more of the total voting power of (x) the corporation resulting from such Business Combination (the

"Surviving Corporation"), or (y) if applicable, the ultimate parent corporation that directly or indirectly has beneficial ownership of 100% the voting securities eligible to elect directors of the Surviving Corporation (the "Parent Corporation"), is represented by Company Voting Securities that were outstanding immediately prior to such Business Combination (or, if applicable, is represented by shares into which such Company Voting Securities were converted pursuant to such Business Combination), and such voting power among the holders thereof is in substantially the same proportion as the voting power of such Company

Voting Securities among the holders thereof immediately prior to the Business Combination, (B) no person (other than any employee benefit plan (or related trust) sponsored or maintained by the Surviving Corporation or the Parent Corporation), is or becomes the beneficial owner, directly or indirectly, of 35% or more of the total voting power of the outstanding voting securities eligible to elect directors of the Parent Corporation (or, if there is no Parent Corporation, the Surviving Corporation) and (C) at least a majority of the members of the board of directors of the Parent Corporation (or if there is no Parent Corporation, the Surviving Corporation) following the consummation of the Business Combination were Incumbent Directors at the time of the Board's approval of the execution of the initial agreement providing for such Business Combination (any Business Combination which satisfies all of the criteria specified in (A), (B) and (C) above shall be deemed to be a "Non-Qualifying Transaction"); or

(iv) stockholder approval of a liquidation or dissolution of the Company, unless the voting common equity interests of an ongoing entity (other than a liquidating trust) are beneficially owned, directly or indirectly, by the Company's shareholders in substantially the same proportions as such shareholders owned the Company's outstanding voting common equity interests immediately prior to such liquidation and such ongoing entity assumes all existing obligations of the Company under this Plan.

Notwithstanding the foregoing, a Change in Control of the Company shall not be deemed to occur solely because any person acquires beneficial ownership of more than 35% of the Company Voting Securities as a result of the acquisition of Company Voting Securities by the Company which reduces the number of Company Voting Securities outstanding; provided, that, if after such acquisition by the Company such person becomes the beneficial owner of Company Voting Securities that increases the percentage of outstanding Company Voting Securities beneficially owned by such person, a Change in Control of the Company shall then occur.

(d) "Code" shall mean the Internal Revenue Code of 1986, as amended.

(e) "Committee" shall mean a committee of at least two members of the Board appointed by the Board to administer the Plan and to perform the functions set forth herein and who are "non-employee directors" within the meaning of Rule 16b-3 as promulgated under Section 16 of the Securities Exchange Act of 1934, as amended (the "Exchange Act") and who are also "outside directors" within the meaning of Section 162(m) of the Code.

(f) "Common Stock" shall mean the common stock of the Company.

(g) "Continuous Service" means that the Participant's service as an employee, director or consultant with the Company or a Subsidiary is not interrupted or terminated. The Participant's Continuous Service shall not be deemed to have terminated merely because of a change in the capacity in which the Participant renders service to the Company or a Subsidiary as an employee, director or consultant or a change in the entity for which the Participant renders such service; provided, that, there is no interruption or termination of the Participant's Continuous Service other than an approved leave of absence. The Committee, in its sole discretion, may determine whether Continuous Service shall be considered interrupted.

(h) "Disability" shall have the same meaning as provided in any long-term disability plan maintained by the Company or any Subsidiary in which a Participant then participates (the "LTD Plans"); provided, that, if no such plan exists, it shall have the meaning set forth in Section 22(e)(3) of the Code.

(i) "Fair Market Value" per share as of a particular date shall mean, unless otherwise determined by the Board, the last reported sale price of the Common Stock on the NASDAQ (or any other exchange or

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national market system upon which price quotations for the Company's Common Stock is regularly available) for such date.

(j) "Immediate Family Member" shall mean, except as otherwise determined by the Committee, a Participant's spouse, ancestors and descendants.

(k) "Incentive Stock Option" shall mean a stock option which is intended to meet the requirements of Section 422 of the Code.

(l) "Nonqualified Stock Option" shall mean a stock option which is not intended to be an Incentive Stock Option.

(m) "Option" shall mean either an Incentive Stock Option or a Nonqualified Stock Option.

(n) "Participant" shall mean anyone who is selected to participate in the Plan in accordance with Section 5.

(o) "Subsidiary" shall mean any affiliate of the Company selected by the Board; provided, that, with respect to Incentive Stock Options, it shall mean any subsidiary of the Company that is a corporation and which at the time qualifies as a "subsidiary corporation" within the meaning of Section 424(f) of the Code.

(p) "Substitute Awards" shall mean Options granted or shares issued by the Company in assumption of, or in substitution or exchange for, awards previously granted, or the right or obligation to make future awards, by a company acquired by the Company or with which the Company is combined.

3. Shares Subject to the Plan.

(a) General. Subject to adjustment in accordance with Section 12, the total of the number of shares of Common Stock which shall be available for the grant of Options under the Plan shall not exceed 3,300,000 shares of Common Stock; provided, that, for purposes of this limitation, any Common Stock subject to an Option which is canceled, forfeited or expires prior to exercise whether such Option was granted under this Plan or the 1998 Non-Qualified Stock Option Plan, as amended, the 1996 Non-Qualified Stock Option Plan, as amended or the 1996 Incentive Stock Option Plan, as amended (together, the "Prior Plans") shall again become available for grant under the Plan. In addition, any shares of Common Stock tendered and/or withheld for the payment of all or a part of an Option (whether granted under this Plan or the Prior Plans) or any applicable withholding taxes shall again become available for the grant of an Option under the Plan. The Company may, but is not required to, use the proceeds it receives in connection with the exercise of an Option under this Plan, or under the Prior Plans for exercises occurring after the Effective Date, to purchase shares of its Common Stock in the open market and any such shares of Common Stock so purchased may be used for the issuance of Options under this Plan. Substitute Options shall not reduce the shares of Common Stock available for grants under the Plan or to a Participant over a period of time. Subject to adjustment in accordance with Section 12, no employee shall be granted, during any three (3) year period, Options to purchase more than 3,300,000 shares of Common Stock.

Common Stock available for issue or distribution under the Plan shall be authorized and unissued shares or shares reacquired by the Company in any manner.

(b) Incentive Stock Options. Notwithstanding Section 3(a), subject to adjustment in accordance with Section 12, the aggregate number of shares of Common Stock with respect to which Incentive Stock Options may be granted under the Plan shall not exceed 825,000 shares of Common Stock. Any shares of Common Stock subject to an Incentive Stock Option granted under this Plan or the 1996 Incentive Stock Option Plan, as amended which is canceled, forfeited or expires prior to exercise shall again be counted toward the aggregate number of shares available for the grant of Incentive Stock Options under this Plan.

4. Administration.

(a) The Plan shall be administered by the Committee. All references to the Committee hereinafter shall mean the Board if no such Committee has been appointed.

(b) The Committee shall (i) approve the selection of Participants, (ii) determine the type of Options to be made to Participants, (iii) determine the number of shares of Common Stock subject to

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Options, (iv) determine the terms and conditions of any Option granted hereunder (including, but not limited to, any forfeiture conditions on such Option) and (v) have the authority to interpret the Plan, to establish, amend, and rescind any rules and regulations relating to the Plan, to determine the terms and provisions of any agreements entered into hereunder, and to make all other determinations necessary or advisable for the administration of the Plan. The Committee may correct any defect, supply any omission or reconcile any inconsistency in the Plan or in any Option in the manner and to the extent it shall deem desirable to carry it into effect.

(c) Any action of the Committee shall be final, conclusive and binding on all persons, including the Company and its Subsidiaries and shareholders, Participants and persons claiming rights from or through a Participant.

(d) The Committee may delegate to officers or employees of the Company or any Subsidiary, and to service providers, the authority, subject to such terms as the Committee shall determine, to perform administrative functions with respect to the Plan and Option awards.

(e) Members of the Committee and any officer or employee of the Company or any Subsidiary acting at the direction of, or on behalf of, the Committee shall not be personally liable for any action or determination taken or made in good faith with respect to the Plan, and shall, to the extent permitted by law, be fully indemnified by the Company with respect to any such action or determination.

5. Eligibility. Individuals eligible to receive Options under the Plan shall be the officers, employees, directors and consultants of the Company and its Subsidiaries selected by the Committee; provided, that, only employees of the Company and its Subsidiaries may be granted Incentive Stock Options.

6. Options. Options may be granted under the Plan in such form as the Committee may from time to time approve pursuant to terms set forth in an Option award.

(a) Types of Options. Each Option award shall state whether or not the Option will be treated as an Incentive Stock Option or Nonqualified Stock Option. The aggregate Fair Market Value of the Common Stock for which Incentive Stock Options granted to any one employee under this Plan or any other incentive stock option plan of the Company or of any of its Subsidiaries may by their terms first become exercisable during any calendar year shall not exceed $100,000, determining Fair Market Value as of the date each respective Option is granted. In the event such threshold is exceeded in any calendar year, such excess Options shall be automatically deemed to be Nonqualified Stock Options. To the extent that any Option granted under this Plan which is intended to be an Incentive Stock Option fails for any reason to qualify as such at any time, such Option shall be a Nonqualified Stock Option.

(b) Option Price. The purchase price per share of the Common Stock purchasable under an Option shall be determined by the Committee and shall not be less than 100% of the Fair Market Value of the Common Stock on the date of grant. In the case of Incentive Stock Options granted to an employee owning stock possessing more than 10% of the total combined voting power of all classes of shares of the Company and its Subsidiaries (a "10% Shareholder") the price per share specified in the agreement relating to such Option shall not be less than 110% of the Fair Market Value per share of the Common Stock on the date of grant.

(c) Option Period. Unless otherwise provided in an Option award, the term of each Option shall be ten (10) years from the date the Option is granted; provided, that, in the case of Incentive Stock Options granted to 10% Shareholders, the term of such Option shall not exceed five (5) years from the date of grant. Notwithstanding the foregoing, unless otherwise provided in an Option award, upon the death or Disability of a Participant, Options (other than Incentive Stock Options) that would otherwise remain exercisable following such death or Disability shall remain exercisable for one year following such death or Disability notwithstanding the term of such Option.

(d) Exercisability. Each Option shall vest and become exercisable at a rate determined by the Committee on the date of grant.

(e) Termination of Continuous Service. Unless otherwise provided in an Option award, any Options held by a Participant upon termination of Continuous Service shall remain exercisable as follows:

(i) If the Participant's termination of Continuous Service is due to death, all unvested Options shall automatically terminate and all vested Options shall be exercisable by the Participant's designated beneficiary, or, if none, the person(s) to whom such Participant's rights under the Option are transferred by will or the laws of descent and distribution for 1 year following such termination of Continuous Service (but in no event beyond the term of the Option, except as provided in clause (c) above), and shall thereafter terminate.

(ii) If the Participant's termination of Continuous Service is due to Disability, all unvested Options shall automatically terminate and all vested Options shall be exercisable by the Participant for 1 year following such Disability (but in no event beyond the term of the Option, except as provided in clause (c) above), and shall thereafter terminate.

(iii) If the Participant's termination of Continuous Service is

for Cause, the Option shall terminate upon such termination of Continuous Service, regardless of whether the Option was then vested and exercisable.

(iv) If the Participant's termination of Continuous Service is for any other reason, all unvested Options shall terminate on the date of termination and all Options (to the extent exercisable as of the date of termination) shall be exercisable for a period of 30-days following such termination of employment or service (but in no event beyond the term of the Option), and shall thereafter terminate. The Participant's status as an employee shall not be considered terminated in the case of a leave of absence agreed to in writing by the Company (including, but not limited to, military and sick leave); provided, that, with respect to Incentive Stock Options, such leave is for a period of not more than three-months or re-employment upon expiration of such leave is guaranteed by contract or statute.

(f) Method of Exercise. Options may be exercised, in whole or in part, by giving written notice of exercise to the Company in a form approved by the Company specifying the number shares of Common Stock to be purchased. Such notice shall be accompanied by the payment in full of the Option exercise price. Unless otherwise provided at the time of grant, the exercise price of the Option may be paid by (i) cash or certified or bank check, (ii) surrender of Common Stock held by the Participant for at least six (6) months prior to exercise (or such longer or shorter period as may be required to avoid a charge to earnings for financial accounting purposes) or the attestation of ownership of such shares, in either case, if so permitted by the Company, (iii) through a "same day sale" commitment from a Participant and a broker-dealer, who is reasonably acceptable to and approved by the Company and who is a member of the National Association of Securities Dealers, under such terms and conditions which are reasonably acceptable to the Company, (iv) through additional methods prescribed by the Committee, as deemed appropriate by the Committee in its discretion, or (v) by any combination of the foregoing, and, in all instances, to the extent permitted by applicable law. A Participant's subsequent transfer or disposition of any Common Stock acquired upon exercise of an Option shall be subject to any Federal and state laws then applicable, specifically securities law, and the terms and conditions of this Plan.

7. Special Provisions.

(a) Change in Control. Unless otherwise provided in an Option award, upon the occurrence of a Change in Control, all Options and shall automatically become vested and exercisable in full. The Committee may, in its discretion, include such further provisions and limitations in any award documenting such Options as it may deem equitable and in the best interests of the Company.

(b) Forfeiture. Notwithstanding anything in the Plan to the contrary and unless otherwise specifically provided in an Option award, in the event of a serious breach of conduct by a Participant or former Participant (including, without limitation, any conduct prejudicial to or in conflict with the Company or its Subsidiary) the Committee may (i) cancel any outstanding Option granted to such Participant or former Participant, in whole or in part, whether or not vested, and/or (ii) if such conduct or activity occurs within one (1) year following the exercise of an Option, require such Participant or former Participant to repay to the

Company any gain realized upon the exercise of such Option (with such gain or payment valued as of the date of exercise). Such cancellation or repayment obligation shall be effective as of the date specified by the Committee. Any

repayment obligation shall be satisfied in cash or, if permitted in the sole discretion of the Committee, it may be satisfied in shares of Common Stock (based upon the Fair Market Value of the share of Common Stock on the date of payment), and the Committee may provide for an offset to any future payments owed by the Company or any Subsidiary to the Participant or former Participant if necessary to satisfy the repayment obligation. The determination of whether a Participant or former Participant has engaged in a serious breach of conduct shall be determined by the Committee in good faith and in its sole discretion.

8. Withholding. Upon (a) disposition of shares of Common Stock acquired pursuant to the exercise of an Incentive Stock Option granted pursuant to the Plan within two years of the grant of the Incentive Stock Option or within one year after exercise of the Incentive Stock Option, or (b) exercise of a Nonqualified Stock Option (or an Incentive Stock Option treated as a Nonqualified Stock Option), or (c) under any other circumstances determined by the Committee in its sole discretion, the Company shall have the right to require any Participant, and such Participant by accepting the Options granted under the Plan agrees, to pay to the Company the amount of any taxes which the Company shall be required to withhold with respect thereto. In the event of clauses (a), (b) or (c), with the consent of the Committee, at its sole discretion, such Participant may elect to have the Company withhold shares of Common Stock having a Fair Market Value equal to the amount of the withholding tax obligation as determined by the Company; provided, however, that no shares of Common Stock are withheld with a value exceeding the minimum amount of tax required to be withheld by law. Such shares so delivered to satisfy the minimum withholding obligation may be either shares withheld by the Company upon the exercise of the Option or other shares. At the Committee's sole discretion, a Participant may elect to have additional taxes withheld and satisfy such withholding with cash or shares of Common Stock held for at least six (6) months prior to exercise, if, in the opinion of the Company's outside accountants, doing so, would not result in a charge against earnings. If the Option is an Incentive Stock Option, and if the Participant sells or otherwise disposes of any of the shares acquired pursuant to the Incentive Stock Option on or before the later of (i) the date two (2) years after the date of grant, and (ii) the date one (1) year after transfer of such shares to the Participant upon exercise of the Option, the Participant shall immediately notify the Company in writing of such disposition.

9. Nontransferability, Beneficiaries. Unless otherwise determined by the Committee with respect to the transferability of Nonqualified Stock Options by a Participant to his Immediate Family Members (or to trusts or partnerships or limited liability companies established for such family members), no Options shall be assignable or transferable by the Participant, otherwise than by will or the laws of descent and distribution or pursuant to a beneficiary designation, and Options shall be exercisable, during the Participant's lifetime, only by the Participant (or by the Participant's legal representatives in the event of the Participant's incapacity). Each Participant may designate a beneficiary to exercise any Option held by the Participant at the time of the Participant's death. If no beneficiary has been named by a deceased Participant, any Option held by the Participant at the time of death shall be transferred as provided in his will or by the laws of descent and distribution. Except in the case of the holder's incapacity, an Option may only be exercised by the holder thereof.

10. No Right to Continuous Service. Nothing contained in the Plan or in any Option under the Plan shall confer upon any Participant any right with respect to the continuation of service with the Company or any of its Subsidiaries, or interfere in any way with the right of the Company or its Subsidiaries to terminate his or her Continuous Service at any time. Nothing contained in the Plan shall confer upon any Participant or other person any

claim or right to any Option under the Plan.

11. Governmental Compliance. Each Option under the Plan shall be subject to the requirement that if at any time the Committee shall determine that the listing, registration or qualification of any shares issuable or deliverable thereunder upon any securities exchange or under any Federal or state law, or the consent or approval of any governmental regulatory body, is necessary or desirable as a condition thereof, or in connection therewith, no such Option may be exercised or shares issued or delivered unless such listing, registration, qualification, consent or approval shall have been effected or obtained free of any conditions not acceptable to the Committee.

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12. Adjustments; Corporate Events.

(a) In the event of any dividend or other distribution (whether in the form of cash, Common Stock, other securities, or other property), recapitalization, reclassification, stock split, reverse stock split, reorganization, merger, consolidation, split-up, spin-off, combination, repurchase, liquidation, dissolution, or sale, transfer, exchange or other disposition of all or substantially all of the assets of the Company, or exchange of Common Stock or other securities of the Company, issuance of warrants or other rights to purchase Common Stock or other securities of the Company, or other similar corporate transaction or event (an "Event"), and in the Committee's opinion, such event affects the Common Stock such that an adjustment is determined by the Committee to be appropriate in order to prevent dilution or enlargement of the benefits or potential benefits intended to be made available under the Plan or with respect to an Option, then the Committee shall, in such manner as it may deem equitable, including, without limitation, adjust any or all of the following: (i) the number and kind of shares of Common Stock (or other securities or property) with respect to which Options may be granted; (ii) the number and kind of shares of Common Stock (or other securities or property) subject to outstanding Options; and (iii) the exercise price with respect to any Option. The Committee determination under this Section 12(a) shall be final, binding and conclusive.

(b) Upon the occurrence of an Event in which outstanding Options are not to be assumed or otherwise continued following such an Event, the Committee may, in its discretion, terminate any outstanding Option (whether or not vested) without a Participant's consent and (i) provide for either (A) the purchase of any such Option for an amount of cash equal to the product of (I) and (II), where (I) is equal to the number of shares of Common Stock subject to such Option and (II) is equal to the difference between (a) the Fair Market Value of one share of Common Stock and (b) the per share exercise price of such Option; provided, that, if such amount would result in a negative number, the Option shall automatically terminate and cease to be exercisable without payment for such termination or (B) the replacement of such Option with other rights or property selected by the Committee in its sole discretion and/or (ii) provide that such Option shall be exercisable (whether or not vested) as to all shares covered thereby for at least thirty (30) days prior to such Event.

(c) The existence of the Plan, the Option awards and the Options granted hereunder shall not affect or restrict in any way the right or power of the Company or the shareholders of the Company to make or authorize any adjustment, recapitalization, reorganization or other change in the Company's capital structure or its business, any merger or consolidation of the Company, any issue of stock or of options, warrants or rights to purchase stock or of bonds, debentures, preferred or prior preference stocks whose rights are superior to or

affect the Common Stock or the rights thereof or which are convertible into or exchangeable for Common Stock, or the dissolution or liquidation of the Company, or any sale or transfer of all or any part of its assets or business, or any other corporate act or proceeding, whether of a similar character or otherwise.

13. Option Awards. Each Option under the Plan shall be evidenced by a written document setting forth the terms and conditions, as determined by the Committee, which shall apply to such Option, in addition to the terms and conditions specified in the Plan.

14. Amendment. The Board may amend, suspend or terminate the Plan or any portion thereof at any time, provided that (a) no amendment shall be made without shareholder approval if such approval is necessary to comply with any applicable law, regulation or stock exchange rule and (b) except as provided in Section 12, no amendment shall be made that would adversely affect the rights of a Participant under an Option theretofore granted, without such Participant's written consent.

15. General Provisions.

(a) The Committee may require each Participant acquiring shares pursuant to an Option under the Plan to represent to and agree with the Company in writing that such Participant is acquiring the shares for investment and without a view to distribution thereof.

(b) All certificates for Common Stock delivered under the Plan pursuant to any Option shall be subject to such stock-transfer orders and other restrictions as the Committee may deem advisable under the rules, regulations, and other requirements of the Securities and Exchange Commission, any stock exchange

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upon which the Common Stock is then listed, and any applicable Federal or state securities law, and the Committee may cause a legend or legends to be put on any such certificates to make appropriate reference to such restrictions. If the Committee determines that the issuance of Common Stock hereunder is not in compliance with, or subject to an exemption from, any applicable Federal or state securities laws, such shares shall not be issued until such time as the Committee determines that the issuance is permissible.

(c) It is the intent of the Company that the Plan satisfy, and be interpreted in a manner that satisfies, the applicable requirements of Rule 16b-3 as promulgated under Section 16 of the Exchange Act so that Participants will be entitled to the benefit of Rule 16b-3, or any other rule promulgated under Section 16 of the Exchange Act, and will not be subject to short-swing liability under Section 16 of the Exchange Act. Accordingly, if the operation of any provision of the Plan would conflict with the intent expressed in this Section 15(c), such provision to the extent possible shall be interpreted and/or deemed amended so as to avoid such conflict.

(d) Except as otherwise provided by the Committee in the applicable Option award, a Participant shall have no rights as a shareholder with respect to any shares of Common Stocks subject to an Option until a certificate or certificates evidencing shares of Common Stock shall have been issued to the Participant and, subject to Section 12, no adjustment shall be made for dividends or distributions or other rights in respect of any share for which the record date is prior to the date on which Participant shall become the holder of record thereof.

(e) The law of the State of Delaware shall apply to all Options and interpretations under the Plan regardless of the effect of such state's conflict of laws principles.

(f) Where the context requires, words in any gender shall include any other gender.

(g) Headings of Sections are inserted for convenience and reference; they do not constitute any part of this plan.

16. Expiration of the Plan. Subject to earlier termination pursuant to Section 14, the Plan shall have an indefinite term; provided, that, the ability to grant Incentive Stock Options will terminate on April 3, 2012 which is the tenth (10th) anniversary of the date on which the Board adopted the Plan.

17. Effective Date; Approval of Shareholders. The Plan is effective as of the date it is approved by the affirmative vote of the holders of a majority of the securities of the Company present, or represented, and entitled to vote at a meeting of stockholders duly held in accordance with the applicable laws of the State of Delaware (the "Effective Date"). If the Plan is approved, no further grants shall be made under the terms of the Prior Plans on or after the Effective Date; provided, that, any outstanding Options made thereunder shall be governed and controlled by the terms and conditions of such Prior Plans and any Option awards evidencing such Options.

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IMCLONE SYSTEMS INCORPORATED

Dear Stockholder,

Please take note of the important information enclosed with this Proxy Ballot. There are a number of issues related to the management and operations of your Company that require your immediate attention and approval. These are discussed in detail in the enclosed proxy materials.

Your vote counts, and you are strongly encouraged to exercise your right to vote your shares.

Please mark the boxes on the proxy card to indicate how your shares should be voted. Then sign the card, detach it and return your proxy vote in the enclosed postage paid envelope. You may also vote your shares by telephone or via the Internet. If you choose to vote by telephone or via the Internet, you do not need to return the attached card.

Your vote must be received prior to the Annual Meeting of Stockholders, May 23, 2002.

Thank you in advance for your prompt consideration of these matters.

Sincerely,

IMCLONE SYSTEMS INCORPORATED

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PROXY

IMCLONE SYSTEMS INCORPORATED

PROXY FOR THE MEETING OF STOCKHOLDERS, MAY 23, 2002
THIS PROXY IS SOLICITED ON BEHALF OF THE BOARD OF DIRECTORS

The undersigned hereby appoints Samuel D. Waksal, Robert F. Goldhammer and Daniel S. Lynch as Proxies, each with power of substitution, and hereby authorizes each of them to represent and to vote, as designated below, all of the shares of Common Stock of ImClone Systems Incorporated held of record by the undersigned on April 16, 2002 at the Annual Meeting of Stockholders on May 23, 2002 and any postponements or adjournments thereof.

PLEASE MARK, SIGN, DATE AND RETURN THIS PROXY TO EQUISERVE, THE COMPANY'S TRANSFER AGENT, TO BE RECEIVED NO LATER THAN MAY 22, 2002.

This Proxy, when properly executed will be voted in the manner directed herein by the undersigned stockholder. IF NO DIRECTION IS MADE, THIS PROXY WILL BE VOTED FOR PROPOSALS 1, 2, 3 AND 4.

IF YOU CHOOSE TO VOTE BY MAIL, PLEASE MARK, DATE, AND SIGN ON REVERSE SIDE AND RETURN PROMPTLY IN THE ENCLOSED ENVELOPE.

HAS YOUR ADDRESS CHANGED?

DO YOU HAVE ANY COMMENTS?

<PAGE>
IMCLONE SYSTEMS INCORPORATED
C/O EQUISERVE
P.O. BOX 43068
PROVIDENCE, RI 02940

VOTE BY TELEPHONE	VOTE VIA THE INTERNET
It's fast, convenient and immediate! Call Toll-Free on a Touch-Tone Phone 1-877-PRX-VOTE (1-877-779-8683)	It's fast and convenient! Your vote is immediately confirmed and posted.
FOLLOW THESE FOUR EASY STEPS:	FOLLOW THESE FOUR EASY STEPS:
1. READ THE ACCOMPANYING PROXY STATEMENT AND PROXY CARD	1. READ THE ACCOMPANYING PROXY STATEMENT AND PROXY CARD.
2. CALL THE TOLL-FREE NUMBER 1-877-PRX-VOTE (1-877-779-8683)	2. GO TO THE WEBSITE HTTP://WWW.EPROXYVOTE.COM/IMCL
3. ENTER YOUR VOTER CONTROL NUMBER LOCATED ON YOUR PROXY CARD YOUR NAME	3. ENTER YOUR VOTER CONTROL NUMBER LOCATED ON YOUR PROXY CARD ABOVE YOUR NAME.
4. FOLLOW THE RECORDED INSTRUCTIONS.	4. FOLLOW THE INSTRUCTIONS PROVIDED.

YOUR VOTE IS IMPORTANT!
Call 1-877-PRX-VOTE anytime!

YOUR VOTE IS IMPORTANT!
Go to http://www.eproxyvote.com/imcl
anytime!

DO NOT RETURN YOUR PROXY CARD IF YOU ARE VOTING BY TELEPHONE OR VIA THE INTERNET.
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[X] PLEASE MARK VOTES AS IN THIS EXAMPLE.

IMCLONE SYSTEMS INCORPORATED

1. Election of Directors.

Nominees: (01) Andrew G. Bodnar, (02) Vincent T. DeVita, Jr., (03) Robert F. Goldhammer, (04) Paul B. Kopperl, (05) David M. Kies, (06) Arnold J. Levine, (07) John Mendelsohn, (08) William R. Miller, (09) Peter S. Ringrose, (10) Harlan W. Waksal, (11) Samuel D. Waksal

For all nominees [ ]

Withheld from all nominees [ ]

[ ] For all nominees except as noted above

		FOR	AGAINST	ABSTAIN
2.	Approval of the ImClone Systems Incorporated 2002 Stock 2002 Stock Option Plan.	[ ]	[ ]	[ ]
3.	Approval of an amendment to the Company's Certificate of Incorporation, as amended, to increase the number of shares of common stock the Company is authorized to issue from 120,000,000 to 200,000,000 shares.	[ ]	[ ]	[ ]
4.	Ratification of the appointment of KPMG LLP to serve as the Company's independent certified public accountants for the fiscal year ending December 31, 2002.	[ ]	[ ]	[ ]
5.	Any other business as may come before the meeting or any postponements or adjournments thereof.			

Mark box at right if you plan to attend the meeting. [ ]

Mark box at right if an address change or comment has been noted on the reverse side of this card. [ ]

NOTE: Please sign exactly as your name(s) appear(s) on the books of the Company. Joint owners should each sign personally. When signing as executor, administrator, attorney, trustee or guardian or as custodian for a minor, please give full title as such. If a corporation, please sign in full corporate name and indicate the signer's office. If a partner, sign the partnership name.

Please be sure to sign and date this Proxy.

Signature: _____ Date: _____

Signature: _____ Date: _____

</TEXT>
</DOCUMENT>
</SEC-DOCUMENT>
-----END PRIVACY-ENHANCED MESSAGE-----

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Clifford Saffron
Sent by: Betsy Farrell
04/25/2002 04:07 PM

To: All
cc:
Subject: New Insider Trading Policy

To: Employees of ImClone Systems Incorporated

From: Clifford R. Saffron
Vice President, Legal and Special General Counsel

Date: April 25, 2002

Re: New Insider Trading Policy

Attached please find a copy of the new ImClone Systems Incorporated Insider Trading Policy (the "Policy"), which was recently adopted by our Board of Directors.

Page 8 of the Policy is an "Acknowledgement" that you are required to sign and return to the Company. In the Acknowledgement, you confirm that you:

1. have read the Policy;
2. understand its contents; and
3. agree to be bound by its terms.

The major changes to the Policy are as follows:

1. ALL employees must receive prior **written** authorization from me before executing any transaction in ImClone securities; and

2. ALL employees must exercise their options and, in the event of sale of the shares, sell their shares through a brokerage firm approved by the Company (an "Approved Broker"). Certain specified officers of the Company must conduct all of their ImClone transactions through an Approved Broker.

The "Blackout" in trading in ImClone securities that has been in effect has now been lifted. Accordingly, subject to your compliance with the Policy, including your obtaining the requisite **written** authorization from me, you may once again transact in ImClone securities. However, I will not authorize any transaction in ImClone securities for any employee unless I have previously received a signed Acknowledgement. Acknowledgements must be returned to either Betsy Farrell, Legal, New York, or Jackie Tanner, Human Resources, New Jersey.

Since the Company is still in the process of designating the Approved Brokers, until such

time as it does, you may continue to transact with a broker of your choice.

Mandatory informational/training sessions relating to the Policy will be announced shortly. In the interim, please feel free to call me at (646) 638-5057 if you have any questions.

Please note that hard copies of this memo and the Insider Trading Policy have also been mailed to your home.

Insider Trading Policy as of 4.25.02.d

Clifford R. Saffron
Vice President - Special General Counsel
ImClone Systems Incorporated
180 Varick Street - 6th Floor
New York, NY 10014
Tel.: (646) 638-5057
Fax: (212) 645-2770
E-mail: csaffron@imclone.com

MISCELLANEOUS POLICIES & PROCEDURES

TRANSACTIONS IN COMPANY SECURITIES & CONFIDENTIALITY

INSIDER TRADING POLICY

Background

I. General Rule

The U.S. securities laws regulate the purchase and sale of securities in the interest of protecting the investing public. U.S. securities laws give the Company, its employees, officers and directors, among others, the responsibility to ensure that information about the Company is not used unlawfully in the purchase and sale of securities.

All employees, officers and directors should pay close attention to the laws against trading on "inside" information. These laws are based upon the belief that all persons trading in a company's securities should have equal access to all "material" information about the company. For example, if an employee of a company knows material, non-public information, that employee is prohibited from buying or selling stock in the company until the information has been disclosed to the public. That is because the employee knows information that will very likely cause the stock price to change, and it would be unfair for the employee to have an advantage that the rest of the investing public does not have. In fact, it is more than unfair, it is fraudulent and illegal. Civil and criminal penalties for this illegal conduct are severe.

The general rule is that it is a violation of the federal securities laws for any person to buy or sell securities if he or she is in possession of material non-public information. Information is "material" if it could affect a person's decision whether to buy, sell or hold the securities. Chances are, if you learn something that leads *you* to want to buy or sell stock, that information will be considered material. It is important to keep in mind that material information is not necessarily information that is certain: information that something is likely to happen, or even just that it may happen, can be considered material. For example, if you found out that a laboratory experiment was a success, or that government regulators had approved a new drug, from which you determined a successful new product might be developed, you would probably be in possession of material information. So, too, if you learned that the Company was in merger or joint venture negotiations, even though the deal had not yet been agreed to, you would be in possession of material information. The SEC takes the view that the mere fact that you know the information is enough to bar you from trading; it is no excuse that your reasons for trading were not based on that information.

Information is "non-public" if it is not reasonably accessible to the investing public. Information may, therefore, still be non-public immediately after the Company has released information through public channels (for instance, a press release), because it may take some time for the information to be broadly disseminated. Therefore, there will be a twenty-four (24) hour waiting period after press releases by the Company before transactions can commence.

Furthermore, it is illegal for any person in possession of material non-public information to provide other people with such information or to recommend that they buy or sell securities (a practice known as "tipping"). The concept of unlawful tipping includes passing on information to friends or family members under circumstances that suggest that you were trying to help them make a profit or avoid a loss. When tipping occurs, both the "tipper" and the "tippee" may be liable for breaking the law, and this liability may extend to all those to whom the tippee passes on the information. Besides being considered a form of insider trading, you should always be careful to avoid discussing sensitive Company information in any place (for instance, at lunch, on public transportation, in elevators, etc.) where such information may be heard by others.

Securities laws also subject "controlling persons" to civil penalties for illegal insider trading by employees. "Controlling Persons" include the Company, and has been interpreted by the SEC to include directors, officers and supervisors. These persons may be subject to fines up to the greater of $1,000,000 or three times the profits earned (or losses avoided) by the insider trader.

The Securities and Exchange Commission, the stock exchanges (including NASDAQ) and plaintiffs' lawyers focus on uncovering apparent insider trading. A breach of the insider trading laws could expose the insider to criminal fines of the greater of $1,000,000 or three times the profits earned or losses avoided and imprisonment up to ten years, in addition to civil penalties (up to three times the profits earned or losses avoided) and injunctive actions. In addition, punitive damages may be imposed under state laws.

If you have any questions or are uncertain about any provisions of the Insider Trading Policy, you should err on the side of caution and consult with Clifford R. Saffron, Special General Counsel.

II. To Whom Does This Policy Apply?

The prohibition against trading on material non-public information applies to transactions in securities by **all employees** (plus consultants and temporary staff), officers and directors, in their personal accounts and any accounts for which they are "beneficial owners".

You become a "beneficial owner" of securities if such securities are held by your spouse, minor children, a relative who shares your home, or other persons if by reason of any contact, understanding or agreement you can obtain from such securities benefits substantially equivalent to those of ownership. You should also consider yourself a beneficial owner of securities you do not own outright if you can revest title in yourself, now or in the future.

III. Other Companies' Securities

The same rules apply to securities of other companies. Employees, officers and directors who learn material non-public information about suppliers, customers, or competitors through their work at the Company should keep it confidential and not buy or sell securities in such companies until the information becomes public. Employees, officers and directors should not give tips about such securities.

IV. Policy

The following policy must be followed in order to ensure compliance with applicable laws and with the Company's Insider Trading Policy.

A. Trading In ImClone Securities – Generally

All ImClone employees, including all officers, and directors must receive prior authorization, in writing, from ImClone's Office of the General Counsel prior to executing any transaction in ImClone securities. The obligation to obtain written approval exists whether or not you think you are in possession of material non-public information.

Requests for authorization to transact in ImClone securities by any employee or officer must be made in writing on the form attached as Exhibit A to this policy and sent for approval to Clifford R. Saffron, Special General Counsel, (646) 638-5057. This includes sales of ImClone stock purchased through the Employee Stock Purchase Plan. Purchases of ImClone stock through the Employee Stock Purchase Plan do not require written authorization. The Company, in its sole discretion, may authorize transactions by an employee or officer in ImClone securities. Such authorization must be in writing and will be valid for only forty-eight (48) hours after the time and date indicated. The exercise of employee stock options (without immediate sale) is not subject to this policy. However, stock acquired upon exercise of employee stock options is subject to this policy and may not be sold without written authorization.

In the event that an employee or officer who is assigned to the Office of the General Counsel seeks trading authorization from the Company pursuant to the terms of the Insider Trading Policy, that person shall submit his/her request for authorization to Daniel S. Lynch, the Chief Financial Officer ("CFO") 646-638-5023 for review and approval. The CFO shall assume the duties normally performed by Clifford R. Saffron in reviewing and authorizing the transaction of that person. To the extent that the CFO seeks legal guidance with respect to such a request, he/she shall consult outside counsel pre-approved by the Company for this purpose.

B. Trading In ImClone Securities Pursuant To A Pre-Arranged Plan

An employee or officer seeking to purchase or sell ImClone securities pursuant to a binding contract or plan, subject to irrevocable instructions to purchase or sell securities on a future date, must not be aware of material, non-public information and must obtain authorization from Clifford R. Saffron in writing prior to entering into such an arrangement – even if the plan does not grant the individual control over the timing of the transaction.

Once an individual, having obtained written authorization, has entered into such a pre-arranged plan, that individual may purchase or sell ImClone securities pursuant to such arrangement without regard to whether he/she is aware of material, non-public information, without obtaining further prior written approval from the Company of such transaction so long as the following conditions are met:

- The individual was not aware of material, non-public information when such individual (1) entered into a binding contract to purchase or sell the security, (2) provided written instructions to another person to execute the trade for such person's account, or (3) adopted a written plan for trading securities.

- The contract, instructions or plan either (1) expressly specifies the amount and price of the ImClone securities to be bought or sold and the date of the transaction, (2) provides a written formula or algorithm, or computer program, for determining the amount, price, and date for the transaction, or (3) does not permit the officer or employee to exercise any subsequent influence over how, when, or whether to effect purchases or sales; provided, in addition, that any other person who did exercise such influence was not aware of material non-public information when doing so.

- The purchase or sale that occurs is pursuant to the prior contract, instruction or plan. A purchase or sale is not pursuant to a contract, instruction, or plan if, among other things, the officer or employee altered or deviated from the contract, instruction, or plan or entered into or altered a corresponding or hedging transaction or position with respect to those securities, or the contract, instruction, or plan to purchase or sell securities was not given or entered into in good faith or was a part of a plan or scheme to evade the prohibition on insider trading.

C. Use of Approved Brokers

The Company has made arrangements with certain brokerage firms (each being an "Approved Broker") to ensure that transactions in ImClone securities, including stock option exercises, are executed in compliance with this policy. A list of Approved Brokers is available from the Office of the General Counsel. Approved Brokers have agreed to provide the Company with copies of all confirmations and statements relating to each stock option exercise and accompanying sale. This will allow the Company to verify that transactions in Company securities conducted by persons subject to this policy are consistent with the terms approved by the Company. Therefore, every transaction involving a stock option exercise and accompanying sale of Company securities shall be effected through an Approved Broker. In the event that you have received authorization to exercise stock options and make an accompanying sale of Company securities but fail to use an Approved Broker, the Company will not receive the confirmations or statements relating to your transaction and will consider you to be in violation of this Policy. If you have obtained authorization to exercise stock options and make an accompanying sale but fail to do so, you must notify the Office of the General Counsel. The failure to complete the transaction within forty-eight (48) hours from receipt of written authorization will result in the invalidation of that authorization.

Certain persons (the "Officer Group") must conduct all of their transactions in ImClone securities through an Approved Broker – whether or not related to a stock option exercise. The Officer Group consists of the officers listed in Exhibit C, and other employees or officers as may be designated and informed of such status from time to time by the Office of the General Counsel. The Company will receive copies of all confirmations and statements relating to each transaction effected by a member of the Officer Group and check them against the Company's internal records authorizing the trade.

D. Trading in Put and Call Options

It is the Company's policy that employees, officers and directors not engage in transactions in options on the Company's stock. The Company believes that the trading by employees, officers and directors in the Company's options is inappropriate because it gives the appearance that they are engaging in short term speculation in the Company's stock.

In accordance with the general policies concerning trading in the Company's securities, employees, officers and directors should not recommend that another person trade in standardized options when he or she has knowledge of material non-public information concerning the Company that has not been disclosed to the public.

This policy does not pertain to employee stock options granted by the Company, since employee stock options cannot be traded before they are exercised. However, stock that was acquired upon exercise of a stock option will be treated like any other stock for the purposes of this policy.

E. Margin Accounts

It is generally the case that securities held in a margin account may be sold by a broker without its customer's consent if the customer fails to meet a margin call. If Company stock is held in a margin account for an employee, officer or director, such a sale may occur at a time when that individual has material non-public information or is otherwise not permitted to trade in Company stock, and could give rise to liability under the securities laws or violate the provisions of the Insider Trading Policy. Therefore, the Company cautions all employees, officers and directors from purchasing Company securities on margin or holding Company securities in a margin account. However, such margin transactions will not be prohibited.

F. Trading in Other Securities

No employee, officer or director should place a purchase or sale order, or recommend that another person place a purchase or sale order, in the securities of another corporation if the employee learns in the course of his or her employment or tenure, confidential information about the other corporation that is likely to affect the value of those securities. It is important to be especially sensitive to transactions in the securities of any other company that has, or is in the process of establishing, a significant business relationship with the Company, whether as customer, supplier, affiliate or the like. For example, it would be a violation of the securities laws if an individual learned through Company sources that the Company intended to purchase assets from another company and then that

individual bought or sold stock in that other company because of the likely increase or decrease in the value of its securities.

G. Blackout Periods

There will be periods of time when it is clear that material non-public information is known by employees, officers and directors of the Company. An example would be the making of a seminal discovery in the Company's science, or significant results in one of its clinical trials, or the pending announcement of an important strategic alliance for the Company. In such cases, the Company may determine that transactions in the Company's securities by employees, officers or directors must be prohibited and therefore there would be a "Blackout" period during which no such transactions could take place.

H. Nondisclosure/No Comment Policy

Material non-public information must not be disclosed to anyone, except to persons with the Company whose positions require them to know it, until it has been publicly released by the Company.

In addition, ImClone has adopted the following no-comment policy.

It is a policy of this Company that officers and employees and representatives of the Company are prohibited from commenting on or responding to inquiries or rumors concerning material prospective developments or transactions involving the Company; that all officers and employees and representatives of the Company are hereby directed to respond to any such inquiry or rumor only with a statement to the effect that it is the policy of the Company not to comment on or respond to inquiries or rumors concerning prospective corporate developments or transactions; and that no information with respect to a prospective development or transaction shall be provided to any member of the media, investment community or general public by any officer or employee or representative of the Company until such time as the Company has made a formal public announcement of the corporate development or transaction. The Company's Vice President of Corporate Development and Investor Relations (Andrea Rabney, (646) 638-5024) is the employee designated by the Company to interact with those who would seek information about the Company, including Shareholders. The best policy when such inquiries are directed to you is to refer them directly to the Vice President of Corporate Development and Investor Relations.

I. Reporting a Breach

Every employee is responsible for reporting a breach of the Company's Insider Trading Policy to the Office of the General Counsel. If you learn of any breach, or potential breach of this policy, contact Clifford R. Saffron, (646) 638-5057, Special General Counsel.

Questions

Any questions regarding this Policy, its interpretation and effect should be referred to Clifford R. Saffron, (646) 638-5057, Special General Counsel.

EXHIBIT B

Additional Procedures For The Office Of The General Counsel and The Finance Department

The Finance Department shall not authorize any transaction in Company securities by any employee, officer or director unless and until it has received a copy of a written authorization from the Office of the General Counsel.

The Finance Department shall maintain arrangements with a group of brokerage firms who have agreed to provide the Finance Department with copies of all confirmations or statements relating to certain transactions in the Company's securities by persons subject to the Company's Insider Trading Policy. This group of brokerage firms shall constitute the Approved Brokers discussed in the Company's Insider Trading Policy and a list identifying the Approved Brokers shall be readily available to all of the employees, officers, and directors of the Company.

If a transaction involves a member of the Approved Broker Group or the exercise of stock options with an accompanying sale, the Office of the General Counsel shall send a copy of the approved form of "Request To Transact In Company Stock" (the "Request") to the Finance Department. The Finance Department shall contact the Approved Broker identified on the Request regarding the transaction and expect to receive a copy of a confirmation or statement from the Approved Broker. If, within 48 hours, the Finance Department has not received (1) a statement or confirmation of the completion of the trade from the Approved Broker or (2) notification from the Office of the General Counsel that the individual who filed the Request will not transact, the Finance Department shall contact the Approved Broker for further information.

In the event that the Approved Broker indicates that it either (1) has not received any orders relating to the Request or (2) provides information which indicates that the orders it received are inconsistent with the terms of the Request approved by the Company, the Finance Department shall immediately notify the Office of the General Counsel for further action.

The Office of the General Counsel shall retain in its records, in accordance with the terms of the Company's document retention policy, all Requests, all documents related to the approval or denial of any Request, and all confirmations or statements provided by any Approved Brokers in relation to any Request.

EXHIBIT C

The Officer Group

Peter Bohlen
Charles Dunne
Paul Goldstein
Michael Howerton
John Landes
Lily Lee
Daniel Lynch
Ron Martell
Michael Needle
Andrea Rabney
Clifford Saffron
Joseph Tamowski
Cathy Vaczy
Harlan Waksal
Samuel Waksal

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02 MAG. 1186

Approved: _____
MICHAEL S. SCHACHTER
Assistant United States Attorney

Before: HONORABLE FRANK MAAS
United States Magistrate Judge
Southern District of New York

UNITED STATES OF AMERICA	SEALED COMPLAINT
- v. -	Violation of 18 U.S.C. §§ 2, 371 and 1621; 15 U.S.C. §§ 78j(b) and 78ff; 17 C.F.R. § 240.10b-5
SAMUEL WAKSAL,	
Defendant.	COUNTY OF OFFENSE: NEW YORK

SOUTHERN DISTRICT OF NEW YORK, ss.:

CATHERINE M. FARMER, being duly sworn, deposes and says that she is a Special Agent of the Federal Bureau of Investigation, and charges as follows:

COUNT ONE

(Conspiracy to Commit Fraud in Connection with the Purchase and Sale of Securities: Samuel Waksal and Tippee No. 1)

The Conspiracy

1. From on or about December 26, 2001, up to and including on or about December 28, 2001, in the Southern District of New York and elsewhere, SAMUEL WAKSAL, the defendant, and others known and unknown, unlawfully, willfully, and knowingly did combine, conspire, confederate and agree together and with each other to commit offenses against the United States, to wit, to commit securities fraud in violation of Title 15, United States Code, Sections 78j(b) and 78ff, and Title 17, Code of Federal Regulations, Section 240.10b-5.

2. It was a part and an object of the conspiracy that SAMUEL WAKSAL, the defendant, and others known and unknown, unlawfully, willfully and knowingly, directly and indirectly, by

use of the means and instrumentalities of interstate commerce, the mails and the facilities of national securities exchanges, did use and employ manipulative and deceptive devices and contrivances, in violation of Title 15, Code of Federal Regulations, Section 240.10b-5, by (a) employing devices, schemes and artifices to defraud; (b) making untrue statements of material facts and omitting to state material facts necessary in order to make the statements made, in the light of the circumstances under which they were made, not misleading; and (c) engaging in acts, practices and courses of business which operated and would and did operate as a fraud and deceit upon ImClone and its shareholders, and other persons and entities, in violation of Title 15, United States Code, Sections 78j(b) and 78ff, and Title 17, Code of Federal Regulations, Section 240.10b-5.

Overt Acts

3. In furtherance of the conspiracy and to effect the illegal objects thereof, the following overt acts, among others, were committed in the Southern District of New York and elsewhere:

a. In or about the late evening of December 26, 2001, SAMUEL WAKSAL, the defendant, in New York, New York, had a telephone conversation with a co-conspirator not named as a defendant in this Complaint ("Tippee No. 1") in Florida.

b. On or about December 27, 2001, Tippee No. 1 had a telephone conversation with a representative of Roth Capital Partners, during which Tippee No. 1 placed an order to sell 50,000 share of ImClone common stock.

c. On or about December 27, 2001, Tippee No. 1 had a telephone conversation with a representative of McDonald Investments, during which Tippee No. 1 placed an order to sell 50,000 share of ImClone common stock.

d. On or about December 27, 2001, Tippee No. 1 had a telephone conversation with a representative of Banc of America Securities, LLC, during which Tippee No. 1 placed an order to sell 10,000 share of ImClone common stock.

e. On or about December 28, 2001, Tippee No. 1 had a telephone conversation with a representative of Roth Capital Partners, during which Tippee No. 1 placed an order to sell 25,000 share of ImClone common stock.

(Title 18, United States Code, Section 371).

COUNT TWO

(Conspiracy to Commit Fraud in Connection with the Purchase and Sale of Securities: Samuel Waksal and Tippee No. 2)

The Conspiracy

5. From on or about December 27, 2001, up to and including December 28, 2001, in the Southern District of New York and elsewhere, SAMUEL WAKSAL, the defendant, and others known and unknown, unlawfully, willfully, and knowingly did combine, conspire, confederate and agree together and with each other to commit offenses against the United States, to wit, to commit securities fraud in violation of Title 15, United States Code, Sections 78j(b) and 78ff, and Title 17, Code of Federal Regulations, Section 240.10b-5.

6. It was a part and an object of the conspiracy that SAMUEL WAKSAL, the defendant, and others known and unknown, unlawfully, willfully and knowingly, directly and indirectly, by use of the means and instrumentalities of interstate commerce, the mails and the facilities of national securities exchanges, did use and employ manipulative and deceptive devices and contrivances, in violation of Title 15, Code of Federal Regulations, Section 240.10b-5, by (a) employing devices, schemes and artifices to defraud; (b) making untrue statements of material facts and omitting to state material facts necessary in order to make the statements made, in the light of the circumstances under which they were made, not misleading; and (c) engaging in acts, practices and courses of business which operated and would and did operate as a fraud and deceit upon ImClone and its shareholders, and other persons and entities, in violation of Title 15, United States Code, Sections 78j(b) and 78ff, and Title 17, Code of Federal Regulations, Section 240.10b-5.

Overt Acts

7. In furtherance of the conspiracy and to effect the illegal objects thereof, the following overt acts, among others, were committed in the Southern District of New York and elsewhere:

a. On or about December 27, 2001, SAMUEL WAKSAL, the defendant, placed a telephone call from New York, New York,

to a co-conspirator not named as a defendant in this Complaint ("Tippee No. 2") in Idaho.

b. On or about December 27, 2001, Tippee No. 2 had a telephone conversation with a representative of Merrill Lynch in New York, New York, during which Tippee No. 2 placed an order to sell 39,472 share of ImClone common stock.

(Title 18, United States Code, Section 371).

COUNTS THREE THROUGH EIGHT

(Securities Fraud)

8. On or about the following dates, SAMUEL WAKSAL. the defendant, unlawfully, willfully and knowingly, directly and indirectly, by use of the means and instrumentalities of interstate commerce, the mails and the facilities of national securities exchanges, did use and employ manipulative and deceptive devices and contrivances, in violation of Title 15, Code of Federal Regulations, Section 240.10b-5, by (a) employing devices, schemes and artifices to defraud; (b) making untrue statements of material facts and omitting to state material facts necessary in order to make the statements made, in the light of the circumstances under which they were made, not misleading; and (c) engaging in acts, practices and courses of business which operated and would and did operate as a fraud and deceit upon ImClone and its shareholders, and other persons and entities, in connection with the following:

COUNT	DATE	ACT
THREE	December 27, 2001	Sale of 39,472 shares of ImClone common stock from an account at Merrill Lynch held in the name of Tippee No. 2
FOUR	December 27, 2001	Attempted sale of 79,797 shares of ImClone common stock transferred to an account at Merrill Lynch held in the name of Tippee No. 2
FIVE	December 27, 2001	Sale of 50,000 shares of ImClone common stock from an account at Roth Capital Partners held in the name of Tippee No. 1

SIX	December 27, 2001	Sale of 50,000 shares of ImClone common stock from an account at McDonald Investments held in the name of Tippee No. 1
SEVEN	December 27, 2001	Sale of 10,000 shares of ImClone common stock from an account at Banc of America Securities held in the name of Tippee No. 1
EIGHT	December 28, 2001	Sale of 25,000 shares of ImClone common stock from an account at Roth Capital Partners held in the name of Tippee No. 1

(Title 15, United States Code, Sections 78j(b) and 78ff; Title 18, United States Code, Section 2; Title 17, Code of Federal Regulations, Section 240.10b-5.)

COUNT NINE

(Perjury)

9. On or about April 1, 2002, and on or about April 18, 2002, in the Southern District of New York and elsewhere, SAMUEL WAKSAL, the defendant, having taken an oath before a competent tribunal, officer and person, in a case in which the law of the United States authorizes an oath to be administered, to wit, in testimony before the United States Securities and Exchange Commission, that he would testify, declare, depose and certify truly, and that any written testimony, declaration, deposition and certificate by him subscribed, would be true, unlawfully, willfully, knowingly, and contrary to such oath, stated and subscribed material matter which he did not believe to be true, to wit, the testimony on or about April 1, 2002, and April 18, 2002, the underlined portions of which he believed to be materially false:

Specification One
(Page 96, Line 19 - Page 97, Line 2)

Q: Why did you want to gift shares to Tippee No. 2?
A: I had told [Tippee No. 2] that I was going to do that for [Tippee No. 2]. I had told [Tippee No. 2] a couple of weeks before that - [Tippee No. 2] lived off of [Tippee No. 2's] ImClone. [Tippee No. 2] had no other real means of support, and I had told [Tippee No. 2] when we had talked earlier in December about [Tippee

No. 2's] financial situation, that I was going to give [Tippee No. 2] more ImClone stock that [Tippee No. 2] could use to live on.

Specification Two
(Page 184, Line 14 - Page 184, Line 24)

Q: The next phone call, 9:22 p.m., who were you calling there?
A: [Tippee No. 1 and another person].
Q: What did you talk about?
A: I didn't. I left a message, I couldn't get a hold of them.
Q: What did you say in your message?
A: "Call me, Sam." I leave [Tippee No. 1] quick messages.
Q: Did you hear back from [Tippee No. 1]?
A: Not that night.

Specification Three
(Page 311, Line 10 - Page 313, Line 8)

Q: Dr. Waksal, I'm handing you what's just been marked as Exhibit 114. Have you ever seen this document before?
A: Yes.
Q: What is it?
A: It's a request to transfer my Merrill account and shares of ImClone to [Tippee No. 2].
. . . .
Q: And the second paragraph says, "It's imperative this transfer take place tomorrow morning, December 27th, first thing." Do you see that?
A: Yes.
Q: Why was it so imperative that the transfer take place?
A: I believe this was just the way this was written, just to make sure that they would do it very quickly. [My accountant] was going away and it was making sure that it was done immediately. I don't believe that there was any imperative associated with it.

Specification Four
(Page 485, Line 19 - Page 485, Line 25)

Q: Did you ever instruct [Tippee No. 1 or Tippee No. 2] to sell their shares of ImClone?
(a) A: No.
Q: Did you ever suggest to any of them that they sell their shares of ImClone?

(b) A: No.

(Title 18, United States Code, Section 1621).

The bases for my knowledge and for the foregoing charge are, in part, as follows:

1. I am a Special Agent of the Federal Bureau of Investigation. I am currently assigned to a criminal squad responsible for investigating securities fraud and related offenses, including insider trading.

2. I have participated in the investigation of this matter, and I am familiar with the information contained in this affidavit based on my own personal participation in the investigation, my review of various documents, records, and reports, and my conversations with other individuals, including other law enforcement officers and representatives of the United States Securities and Exchange Commission (the "SEC"). Because this affidavit is submitted for the limited purpose of establishing probable cause to arrest SAMUEL WAKSAL, the defendant, I have not included herein the details of every aspect of the investigation. Where actions, conversations and statements of others are related herein, they are related in substance and in part, except where otherwise indicated.

ImClone Systems, Inc.

3. Based on my review of publicly-available documents, I am aware that ImClone Systems Incorporated ("ImClone") is a corporation organized under the laws of the State of Delaware with its principal place of business in New York, New York. ImClone is engaged in the business of developing biologic medicines, including the development of Erbitux, a biologic treatment for irinotecan-refractory colorectal cancer. ImClone has described Erbitux as its lead product candidate. ImClone's common stock is listed on the NASDAQ National Market System, an electronic market system administered by the National Association of Securities Dealers, under the symbol "IMCL." Until May 22, 2002, when he resigned, SAMUEL WAKSAL, the defendant, was president, chief executive officer, and a director of ImClone.

Samuel Waksal's Financial Condition

4. Based on brokerage records I have reviewed and a conversation that I have had with a representative of Banc of

America Securities, LLC, I have learned that as of December 26, 2001, SAMUEL WAKSAL, the defendant, had over $80 million in indebtedness, over $65 million of which was "margin debt" secured by his shares of ImClone stock. At that time, SAMUEL WAKSAL was required to pay over approximately $800,000 each month to service his indebtedness.

ImClone's Policies on Insider Trading

5. Based on documents I have reviewed, I have learned that at all times relevant to this Complaint, ImClone distributed memoranda advising its officers and employees of their responsibilities under the federal securities laws. In or about April 2001 and in preceding years, ImClone distributed a memorandum advising employees of its insider trading policy, which stated in part:

> U.S. securities laws give the Company, its directors, officers and other employees, among others, the responsibility to ensure that information about the Company is not used unlawfully in the purchase and sale of securities.
>
> All directors, officers and other employees should pay close attention to the laws against trading on "inside" information. These laws are based upon the belief that all persons trading in a company's securities should have equal access to all "material" information about the company. For example, if an employee of a company knows material, non-public information, that employee is prohibited from buying or selling stock in the company until the information has been disclosed to the public. That is because the employee knows information that will very likely cause the stock price to change, and it would be unfair for the employee to have an advantage that the rest of the investing public does not have. In fact, it is more than unfair, it is fraudulent and illegal
> . . . .
>
> The general rule is that it is a violation of the federal securities laws for any person to buy or sell securities if he or she is in

> possession of material inside information. Information is "material" if it could affect a person's decision whether to buy, sell or hold the securities. It is "inside" information if it has not been publicly disclosed. Furthermore, it is illegal for any person in possession of material inside information to provide other people with such information or to recommend that they buy or sell the securities ("tipping"). In that case, they may both be held liable . . . .

6. Based on documents I have reviewed, I have learned that ImClone also established so-called "Blackout Periods" during which its officers and employees were prohibited from engaging in any transactions in ImClone common stock. The Blackout Period was described to ImClone personnel in a memorandum. The memorandum further instructed directors and officers not to execute any transaction in ImClone stock during a Blackout Period without first receiving authorization from ImClone's Office of the General Counsel. Publicly-traded companies often adopt such policies to prevent officers and employees from trading in the company's stock during periods in which officers and employees have access to material, non-public information.

The Insider Trading Scheme

SAMUEL WAKSAL's Acquisition of Inside Information

7. Based on documents I have reviewed, I have learned that on or about October 31, 2001, ImClone submitted to the United States Food and Drug Administration (the "FDA") a Biologics Licensing Application ("BLA") for approval of Erbitux (the "Erbitux BLA"). Based on my conversations with a representative of the FDA, I am aware that the FDA has 60 days from the date a BLA is submitted to decide whether the BLA is administratively and scientifically complete to accept the BLA for FDA review. Only if a BLA is accepted for filing does the FDA review the application to determine whether the treatment will be approved. Because Erbitux was ImClone's lead product candidate, I believe that information regarding the FDA's decision on the Erbitux BLA would be material to investors in ImClone stock.

8. I have reviewed an email distributed by ImClone's Office of the General Counsel to all ImClone employees on December 21, 2001, which placed into effect a "company-wide

blackout in trading in ImClone stock." The email stated that "the FDA is required to tell us by the end of next week whether the filing of our BLA for Erbitux has been accepted and whether the file will be granted expedited review," and "[g]iven the importance of this news, we believe employees should not trade in ImClone stock until we receive definitive information from the FDA and a press release is issued."

9. I have reviewed testimony before the SEC given on March 7, 2002 by Harlan Waksal, the brother of SAMUEL WAKSAL, the defendant, who was then ImClone's executive vice-president, chief operating officer, and a director of ImClone, in which Harlan Waksal testified, in substance and in part, that on December 25, 2002, he was informed that a source within the FDA stated that it was "99 percent likely" that ImClone would receive a "Refusal To File Letter" from the FDA on December 28, 2001, in which the FDA would advise ImClone that it had refused to accept the Erbitux BLA for filing.

10. I have reviewed testimony before the SEC given by SAMUEL WAKSAL, the defendant, in which he testified, in substance and in part, that on December 26, 2001, at approximately 6:00 p.m. or 7:00 p.m., he learned that a source within the FDA stated that ImClone was expected to receive a Refusal to File Letter from the FDA on December 28, 2001.

11. Based on my training and experience, I submit that there is probable cause to believe that the FDA's decision to reject the Erbitux BLA was information that was material to investors.

The Illicit Trading

Trading By Tippee No. 1

12. I have reviewed telephone records that reflect the following telephone calls in the late evening of December 26, 2001:

Time of Call	From	To	Length of Call
9:52 p.m.	Samuel Waksal's cell phone	Tippee No. 1's home phone	2 seconds
9:56 p.m.	Samuel Waksal's cell phone	Tippee No. 1's home phone	7 seconds

10:26 p.m.	Samuel Waksal's cell phone	Tippee No. 1's home phone	22 seconds
10:41 p.m.	Tippee No. 1's home phone	Samuel Waksal's home phone	1 minute, 3 seconds
11:11 p.m.	Tippee No. 1's home phone	Samuel Waksal's home phone	42 seconds

13. Based on my review of telephone and brokerage firm records gathered during the course of this information, I am aware that Tippee No. 1 made the following telephone calls placing the following orders to sell ImClone stock in accounts held in the name of Tippee No. 1 (except where otherwise noted) in the morning of December 27, 2001:

Date and Time	From	To	No. of Shares Sold	Proceeds
12/27/01 9:04 a.m.	Tippee No. 1's cell phone	Roth Capital Partners	50,000 shares	$3,062,542
12/27/01 9:09 a.m.	Tippee No. 1's cell phone	McDonald Investment	50,000 shares	$3,088,068
12/27/01 9:27 a.m.	Tippee No. 1's home phone	Prudential Securities	1,336 shares in account in the name of another individual	$83,166
12/27/01 9:41 a.m.	Tippee No. 1's home phone	Banc of America Securities, LLC	10,000 shares	$618,479
12/28/01 9:29 a.m.	Tippee No. 1's home phone	Roth Capital Partners	25,000 shares	$1,429,750

Trading By Tippee No. 2

14. Based on conversations I have had with a representative of the SEC, I have learned that on March 5, 2002, Tippee No. 2 appeared before the SEC pursuant to subpoena in New

York, New York, and gave investigative testimony under oath. I have reviewed Tippee No. 2's testimony. In that testimony, Tippee No. 2 testified that Tippee No. 2 was on vacation in Sun Valley, Idaho on December 27, 2001.

15. Based on telephone and brokerage records I have reviewed, I am aware that on December 27, 2001, at approximately 7:01 a.m. (MST) (9:01 a.m. (EST)), Tippee No. 2 placed an order to sell all of Tippee No. 2's ImClone common stock, consisting of approximately 39,472 shares, yielding proceeds of approximately $2,472,837.

16. I have reviewed telephone records showing that early in the morning of December 27, 2001, just prior to Tippee No.2's sale of all of Tippee No. 2's ImClone stock, numerous telephone calls were placed between telephones associated with SAMUEL WAKSAL and Tippee No. 2:

Time of Call	From	To	Length of Call
6:27 a.m. (MST)	Samuel Waksal's work phone	Tippee No. 2's cell phone	Unknown
6:30 a.m. (MST)	Tippee No. 2's cell phone	Samuel Waksal's work phone	2 minutes
6:58 a.m. (MST)	Tippee No. 2's hotel phone	Samuel Waksal's work phone	2.4 minutes
7:01 a.m. (MST)	Tippee No. 2's hotel phone	Merrill Lynch	1.4 minutes
7:46 a.m. (MST)	Tippee No. 2's hotel phone	Samuel Waksal's work phone	1.3 minutes
7:49 a.m. (MST)	Tippee No. 2's hotel phone	Merrill Lynch	0.7 minutes

Samuel Waksal's Attempted Insider Trading

17. I have spoken with the accountant for SAMUEL WAKSAL, the defendant, who informed me, in substance and in part, that in the evening of December 26, 2001, SAMUEL WAKSAL directed him to cause all of the ImClone common stock in SAMUEL WAKSAL's Merrill Lynch account, 79,797 shares, to be transferred to Tippee No. 2. I have reviewed a letter sent by facsimile from SAMUEL WAKSAL's accountant to SAMUEL WAKSAL on December 26, 2001, at approximately 9:53 p.m., in which the accountant forwarded a

letter to Merrill Lynch to effect the transfer and stated: "I understand that ImClone will have a 'blackout' beginning Friday, therefore, you should make sure that this is completed EARLY tomorrow morning. You have been previously informed regarding 'gift tax' issues, so I won't go into them again."

18. Based on my review of documents and conversations with representatives of Merrill Lynch, I have learned that in the morning of December 27, 2001, SAMUEL WAKSAL, the defendant, directed Merrill Lynch to transfer all of his ImClone common stock held at Merrill Lynch, approximately 79,797 shares then worth approximately $4.9 million, to Tippee No. 2 (the "79,797 shares"). SAMUEL WAKSAL's written direction to Merrill Lynch stated that the transfer request was "URGENT - IMMEDIATE ATTENTION REQUIRED" and that it was "imperative" that the transfer take place in the morning of December 27, 2001. Based on conversations I have had with SAMUEL WAKSAL's accountant, I have learned that subsequent to the transfer of the 79,797 shares, SAMUEL WAKSAL directed his accountant to seek to have the 79,797 shares sold. Based on conversations I have had with a representative of Merrill Lynch and SAMUEL WAKSAL's accountant, I have learned that Merrill Lynch refused to sell the 79,797 shares absent approval from ImClone's Office of the General Counsel because the shares were originally owned by SAMUEL WAKSAL and were subject to restrictions on trading.

19. Based on conversations I have had with SAMUEL WAKSAL's accountant and documents I have reviewed, I have learned that after SAMUEL WAKSAL, the defendant, was informed that Merrill Lynch refused to sell the 79,797 shares, on December 28, 2001, he directed his accountant to transfer the 79,797 shares to Banc of America Securities, LLC. On December 28, 2001, at approximately 2:12 p.m., SAMUEL WAKSAL's accountant informed SAMUEL WAKSAL by email that "B of A consider[s] [Tippee No. 2] an affiliate of ImClone and cannot sell the shares absent company approval."

Public Announcement of the FDA Decision

20. Based on documents I reviewed, I have learned that on December 28, 2001, at approximately 2:55 p.m., the FDA sent a letter to ImClone via facsimile notifying ImClone that the FDA refused to accept the Erbitux BLA for filing. After the close of business on December 28, 2001, ImClone issued a press release announcing that the FDA had refused to accept the Erbitux BLA for filing.

21. From its closing price of 55.25 on December 28, 2001, the price of ImClone stock fell 16% to 46.46 by the close of the next trading day, December 31, 2001.

Concealment of Insider Trading

22. Based on conversations I have had with an attorney with the SEC, I have learned that in or about January 2001, the New York Office of the SEC commenced an investigation to determine whether SAMUEL WAKSAL and members of his family violated the securities laws prohibiting trading while in possession of material, non-public information. I am informed that it was material to the SEC's investigation to determine, among other things, the reasons for the trading, transfers of stock, and attempted trading discussed above.

23. Based on conversations I have had with an attorney with the SEC, I have learned that on April 1, 2002 and April 18, 2002, SAMUEL WAKSAL, the defendant, appeared before the SEC pursuant to subpoena in New York, New York, and gave investigative testimony under oath. I have reviewed SAMUEL WAKSAL's testimony, including the testimony described in Specifications One through Six of Count Nine above. In his testimony, SAMUEL WAKSAL testified, in substance and in part, that:

a. SAMUEL WAKSAL did not speak with Tippee No. 1 during the night of December 26, 2001; did not instruct Tippee No. 1 to sell ImClone stock; and did not suggest to Tippee No. 1 that Tippee No. 1 should sell ImClone stock;

b. SAMUEL WAKSAL did not speak with Tippee No. 2 from the time he heard the report of the FDA's anticipated negative decision until the night of December 27, 2001; did not instruct Tippee No. 2 to sell ImClone stock; and did not suggest to Tippee No. 2 that Tippee No. 1 should sell ImClone stock;

c. SAMUEL WAKSAL had planned to transfer the 79,797 shares to Tippee No. 2 weeks before the transfer; did not believe there was any imperative associated with the transfer of the 79,797 shares to Tippee No. 2; and did not ask to have the 79,797 shares sold.

24. Based on conversations I have had with an attorney with the SEC, I have learned that on March 5, 2002, Tippee No. 2 appeared before the SEC pursuant to subpoena in New York, New York, and gave investigative testimony under oath. I have

reviewed Tippee No. 2's testimony. In that testimony, Tippee No. 2 testified in substance and in part that Tippee No. 2 did not speak to anyone before placing the order to sell ImClone shares and did not discuss with SAMUEL WAKSAL investments in any way during Tippee No. 2's vacation to Idaho.

25. In his testimony, SAMUEL WAKSAL, the defendant, was also asked if he had any interest in any offshore accounts at all, and answered only that he did not know whether Diaz & Altschul, a merchant banking partnership in which he invested, had such an account, and that Scientia Health Group, Inc., a corporation in which SAMUEL WAKSAL had an interest, was a Bermuda corporation.

26. I have reviewed documents, however, reflecting the following regarding SAMUEL WAKSAL's apparent interest in an offshore account:

a. On November 7, 2000, SAMUEL WAKSAL transferred 120,000 restricted shares of ImClone stock, worth approximately $7.5 million to Protec Advisory Group Ltd. ("Protec");

b. On January 5, 2001, Protec, a British Virgin Islands corporation, wire transferred $389,962 to SAMUEL WAKSAL's account at Bank of New York;

c. On May 10, 2001, SAMUEL WAKSAL directed an individual in Switzerland (the "Swiss Individual") to wire transfer $109,300 from "my account" in the "name of: Discount Bank and Trust Company, Geneva" to SAMUEL WAKSAL's account at Bank of New York, which resulted in a wire transfer of $109,300 from an account in the name of Protec;

d. On September 25, 2001, SAMUEL WAKSAL directed $2 million to be wire transferred from his account at Smith Barney to an account at Discount Bank and Trust Company - Amsterdam in the name of Protec for the purpose of purchasing ImClone stock;

e. On November 15, 2001, $1.5 million was wire transferred from an account in the name of Protec at Discount Bank & Trust Company to an account in the name of SAMUEL WAKSAL at First Republic Bank;

27. I have reviewed SAMUEL WAKSAL's business telephone records, which reflect calls to a telephone number in Switzerland

on December 27, 2001, at approximately 10:14 a.m., and on December 28, 2001, at approximately 11:42 a.m., the same dates as the illicit trading described above. In his testimony, SAMUEL WAKSAL identified those calls as being placed to the Swiss Individual. WAKSAL did not state that the Swiss Individual had any connection to Protec, but rather stated that the Swiss Individual "works in the high-tech field" and "we were trying to fund a company called V-Target;" he "could have been calling about V-Target and some Israeli stuff to someone in Switzerland."

WHEREFORE, deponent prays that the above-named individual be arrested and imprisoned or bailed as the case may be.

CATHERINE M. FARMER
Special Agent
Federal Bureau of Investigation

Sworn to before me this
12th day of June, 2002

/s/ Frank Maas
UNITED STATES MAGISTRATE JUDGE
SOUTHERN DISTRICT OF NEW YORK

FRANK MAAS
United States Magistrate Judge
Southern District of New York

Based on the confidential ongoing nature of this investigation, I respectfully request that this Complaint and any warrant issued thereon be filed under seal.

MICHAEL S. SCHACHTER
Assistant United States Attorney

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Slobodin, Alan

From: Santino Fred Civ ESC/CX [Fred.Santino@hanscom.af.mil]
Sent: Friday, June 14, 2002 12:40 PM
To: Slobodin, Alan
Subject: Revised Statement

Rep. James C. Greenwood, Oversight Subcommittee
RE: Imclone Investigation

I'm submitting a statement to your committee to assist in your investigation of Imclone. My wife Ruth-Ann was the subject of Lesley Stahl's "60 Minutes"; story on "Compassionate Use." Ruth-Ann, 51, died of colorectal cancer on 5/5/2001 following an unsuccessful attempt to obtain C-225 (Erbitux) from Imclone. My wife wrote Imclone repeatedly for 3 months on the advice of her doctors at Dana Farber Cancer Center. Ruth-Ann had qualified for other experimental treatment options, but doctors advised her to pursue Imclone's C-225 first. At that time the Imclone web site and their " hotline" said C-225 was available. I wrote several letters myself as did my two
sons. None of our letters were ever answered.

Two days before Ruth-Ann died, Dr. Harlan Waksal called my house to complain that "I was being unfair to Imclone by going on 60 Minutes." He wanted me to stop the show from running. Dr. Waksal never asked how Ruth-Ann was doing, even though he shoiuld have known her condition was critical after two years of cancer. I find it shocking that the lives of desperate
patients must depend on someone who has no awareness of what a cancer patient is
undergoing.

When I learned that Sam Waksal was arrested, I wasn't surprised, as I felt that Waksal's call to me was only the "tip of the iceberg." Imclone has shown me
absolutely no concern for cancer patients, no urgency to expedite Erbitux (C-225) to the market (it's been around since 1995 with a patent). During a hearing of the House Government Reform Committee (6/20/2001), Dr. Waksal tried to change
the facts about Imclone's compassionate use program, saying it had been closed in
January, even though it was listed as being open on the website as of the 60 Minutes show
(I showed this to Lesley Stahl to confirm this).
C-225 was also being promised on the telephone "hotline" long after Dr, Waksal told Cong. Dan Burton's Committee that the program had been closed. Dr.
Waksal further said that he had "so many letters from patients that he couldn't answer them."
We would have appreciated a prompt "no" from Imclone in January 2001, so that Ruth-Ann could pursue another treatment option at Memorial-Sloan Kettering Cancer Center,
New York. Based on Waksal's 6/20/2001 testimony, it was clear that Imclone never sought outside help to
resolve the problem, either trying to answer the letters, or of trying to produce more of the drug. It appears to me that the Waksal brothers were concentrating on the stock market at the expense of helping patients. It also apears to me that the Waksal brothers have no business ethics and displayed a lack of management expertise. Since Imclone has not tested the drug randomly, avoiding people like my wife, one has to question their testing
process, and wonder whether the drug can be confirmed to be effective.

I am continuing to help cancer patients directly and through cancer

c ganizations, both nationally and locally.
I'm helping cancer organizations such as the Virginia-based Abigail Alliance,
and helped obtain funding for the Center for Cancer Support and Education, Arlington, MA.
I'm doing fund raising for scholarships for needy children in my wife's name. I also provide information to cancer patients via a web site based on my 3
years of research.

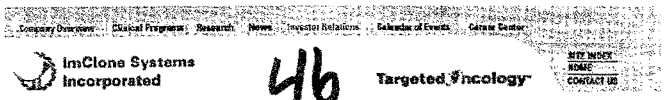
http://hometown.aol.com/cancerhelp1/index.html
I also speak frequently on the subject to help families suffering with cancer.

I have not seen any evidence of similar interest in helping cancer patients on the part of Imclone.

I further certify these statements are true and and are intended to provide additional facts and information to help the committee. I would be willing to answer any further questions if the committee could use my help.

Sincerely,

Fred Santino
4 Littlejohn Street
Arlington, MA 02474
Work Phone 781-377-4518
Home Phone 781-646-4199



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ImClone Systems Incorporated (ticker: IMCL, exchange: NASDAQ) News Release - 6/19/02

ImClone Systems Receives 'Wells Notice' From Securities and Exchange Commission

NEW YORK, Jun 19, 2002 (BW HealthWire) -- ImClone Systems Incorporated (NASDAQ: IMCL) announced that it today received a written "Wells Notice" from the staff of the Securities and Exchange Commission (SEC), indicating that the staff is considering recommending the Commission bring an action against the Company relating to the Company's disclosure immediately following its receipt of a Refusal-to-File letter from the FDA on December 28, 2001 for its biologics license application for ERBITUX.

Under the Wells process established by the Commission, the Company has the opportunity to respond in writing to the "Wells Notice" before the staff makes a formal recommendation regarding what action, if any, should be brought against the Company by the Commission. The Company intends to respond promptly and thoroughly.

The Company reiterates its intention to cooperate fully with the SEC in the course of its investigation.

ImClone Systems Incorporated is committed to advancing oncology care by developing a portfolio of targeted biologic treatments, designed to address the medical needs of patients with a variety of cancers. The Company's three programs include growth factor blockers, cancer vaccines and angiogenesis inhibitors. ImClone Systems' strategy is to become a fully integrated biopharmaceutical company, taking its development programs from the research stage to the market. ImClone Systems is headquartered in New York with additional administration and manufacturing facilities in Somerville, New Jersey.

The matters discussed in this news release may include forward-looking statements which involve potential risks and uncertainties. Important factors that may cause actual results to differ materially include, but are not limited to, the risks and uncertainties associated with completing preclinical and clinical trials of the Company's compounds that demonstrate such compounds' safety and effectiveness; obtaining additional financing to support the Company's operations; obtaining and maintaining regulatory approval for such compounds and complying with other governmental regulations applicable to the Company's business; obtaining the raw materials necessary in the development of such compounds; consummating collaborative arrangements with corporate partners for product development; achieving milestones under collaborative arrangements with corporate partners; developing the capacity to manufacture, market and sell the Company's products, either directly or with collaborative partners; developing market demand for and acceptance of such products; competing effectively with other pharmaceutical and biotechnological products; obtaining adequate reimbursement from third party payers; attracting and retaining key personnel; obtaining patent protection for discoveries and risks associated with commercial limitations imposed by

patents owned or controlled by third parties. The Company does not undertake any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise.

CONTACT: ImClone Systems Incorporated Investors: Andrea F. Rabney, 646/638-5058 or Abernathy MacGregor Media: Andrew Merrill / David Pitts, 212/371-5999

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ONE HUNDRED SEVENTH CONGRESS

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U.S. House of Representatives
Committee on Energy and Commerce

Washington, DC 20515–6115

W.J. "BILLY" TAUZIN, LOUISIANA,
CHAIRMAN

June 27, 2002

Lester M. Crawford, D.V.M., Ph.D.
Deputy Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Crawford:

On June 13, 2002, the Subcommittee on Oversight and Investigations held a hearing concerning the events surrounding the accelerated-approval submission to, and the refusal-to-file decision by, the Food and Drug Administration (FDA) in response to the Biologics Licensing Application (BLA) of Erbitux, a monoclonal antibody biologic developed by ImClone Systems for third-line treatment of colorectal cancer. In so doing, this Committee examined the drug approval process at FDA's Center for Biologics Evaluation and Research (CBER).

While the evidence presented in the hearing record supports the justification for FDA's action in refusing to file the BLA for Erbitux, the hearing also showed that the fast-track process in CBER needed improvement. Further, the Subcommittee learned from the testimony of Dr. Richard Pazdur, the Director of the Division of Oncology Drug Products at the Center for Drug Evaluation and Research (CDER), that there appears to be a different and better approach to the expedited review of cancer drugs at CDER.

There are differences between small molecule drugs and biologics that require different expertise in the review process. FDA, however, uses the same advisory committee to advise the agency about clinical efficacy data for both cancer drugs and biologics, including the data submitted in abbreviated reviews designed to get promising compounds to market quickly when there is an unmet medical need for a life-threatening or otherwise serious illness. Therefore, as FDA strives for a consistent efficacy standard between cancer drugs and biologics, we believe there should be a consistent approach to facilitating expedited reviews of cancer drugs and biologics.

Using Special Protocol Assessments for the design of the registration study or studies makes sense, yet has only been employed once by CBER. The design of a well-controlled study agreed to by the sponsor and the agency in advance of the conduct of a pivotal trial appears to be particularly important when the study employs surrogate

endpoints and/or is done in a very small population. Both of these limitations characterized the studies at the heart of the expedited approval, fast-track submission by ImClone.

Funds have been provided under PDUFA III for management review aimed at, among other goals, coordination of the review processes at CBER and CDER. It would appear that instituting common "best practices" procedures for drugs slated for accelerated approval, at least in the area of protocols for clinical studies and evaluation of the clinical data flowing therefrom, for cancer drugs and perhaps other vital medications could and should be done without extensive study or delay.

It is important that we understand what, if any, obstacles prevent the implementation of the common-sense use of Special Protocol Assessments approach to protocol development and clinical review in CBER. Accordingly, we request that Center Directors Janet Woodcock and Kathryn Zoon, together with such supporting personnel as they may need, meet with Committee staff to discuss the administrative steps that the Centers are prepared to take to assure that protocols of registration studies are properly designed and that the presentation format and content requirements are clear to sponsors and consistent among Centers (including CDRH for combination products that have a device component).

Dr. Pazdur's testimony also showed there are different approaches between CDER and CBER relating to the communications with sponsors about refusal-to-file letters or other negative decisions. We also request that the Center Directors discuss the merits of instituting a best practice procedure regarding communications with sponsors. It appears that early and frequent communications with sponsors result in better decision-making at FDA.

The Committee must also evaluate what, if any, legislation might be necessary or helpful in promoting coordination of the Centers to assure that innovative therapies for unmet medical needs reach desperate patients quickly. Hence it is important that Directors Woodcock and Zoon be prepared to discuss all aspects of the accelerated approval process.

To make arrangements for the meetings or to answer any questions you may have regarding the issues raised by this letter or the ImClone investigation, please contact Alan Slobodin of the Committee Majority staff at 202-225-2927 or David Nelson of the Committee Minority staff at 202-226-3400.

Sincerely,

W.J. "Billy" Tauzin
Chairman

John D. Dingell
Ranking Member

Michael Bilirakis
Chairman
Subcommittee on Health

Sherrod Brown
Ranking Member
Subcommittee on Health

James D. Greenwood
Chairman
Subcommittee on Oversight
and Investigations

Peter Deutsch
Ranking Member
Subcommittee on Oversight
and Investigations

The Washington Post

June 30, 2002, Sunday, Final Edition

Correction Appended

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SECTION: A SECTION; Pg. A01

LENGTH: 3298 words

HEADLINE: A Hospital's Conflict Of Interest; Patients Weren't Told Of Stake in Cancer Drug

BYLINE: Justin Gillis, Washington Post Staff Writer

BODY:

One of the nation's largest cancer centers enrolled 195 people in tests of an experimental drug without informing them that the institution's president held a financial interest in the product that stood to earn him millions.

The tests at M.D. Anderson Cancer Center in Houston involved Erbitux, the controversial cancer drug that is at the center of broad investigations in New York and Washington. Most of the patients, who were quite ill by the time they enrolled in the tests, have died.

The cancer center, a unit of the University of Texas system, has since acknowledged that it should have informed the patients of the conflict of interest involving its president, John Mendelsohn. It has recently adopted policies to ensure that patients are told ahead of time if Mendelsohn or the cancer center itself has a financial stake. Ethicists say that such conflicts of interest pose risks to patients and to the integrity of scientific studies.

A June 30 article about the president of the M.D. Anderson Cancer Center and his financial interest in a drug being tested there mentioned a Seattle Times report about drug testing at the Fred Hutchinson Cancer Research Center. The story said that several Hutchinson doctors "had a financial stake in the outcome" of that research. A senior official at Hutchinson denies that the doctors had a financial interest, saying they had "foreclosed any possibility of commercializing the results of these trials by publishing their research in professional journals rather than seeking patent protection." The Seattle Times has quoted patent attorneys as saying the doctors could have won patent protection later and thereby profited from the research.Erbitux is at the center of an unfolding scandal involving stock trades by executives of the company sponsoring its development, ImClone Systems Inc. One of them was charged with illegal trading. Lifestyle guru Martha Stewart is under investigation for a stock sale she made the day before bad news came out about the drug.

The way Erbitux was tested at M.D. Anderson highlights a different issue: growing conflicts of interest in medical research that could affect any American touched by serious illness.

Genetic research is making possible a burst of medical innovation that promises new treatments, even cures, for serious illnesses such as cancer. But that same research has led to growing ties between academic doctors who invent new drugs and corporations that sponsor their development. What happened at M.D. Anderson, one of the country's most prestigious medical centers, is a case study in the ethical problems such links can pose.

Mendelsohn has been under scrutiny in recent months for his role in two simultaneous business disasters. One involved Enron Corp., the Houston energy trader now in bankruptcy protection -- Mendelsohn served as a director and member of Enron's audit committee. The other involved ImClone, a New York biotechnology company. Mendelsohn invented the company's leading drug, Erbitux, and served on its board.

ImClone is the lesser of the two debacles, but it has caused pain for numerous investors in recent months. ImClone stock, riding high most of last year on the basis of upbeat proclamations from the company, plunged in December after the Food and Drug Administration rejected ImClone's application for approval of the drug, known variously as C225, cetuximab or Erbitux. The FDA cited serious flaws in the company's tests at another facility.

Though Mendelsohn's financial ties to the company and the $6 million he made in an ImClone stock deal last year have been widely reported, his institution's failure to inform cancer patients of those ties has not been.

Details come from hundreds of pages of M.D. Anderson records, released under Texas public-information law, and from interviews in Texas, New York and Washington.

On the basis of the available material, which does not include patient medical records, there is no reason to believe any patient at M.D. Anderson was harmed by taking the drug, which studies indicate is relatively safe.

At the same time, there is no way to know whether any of the 195 patients who enrolled in Erbitux tests from 1997 to 2001, had they been informed of Mendelsohn's financial stake, might have chosen to take a different drug -- or might have fared better as a result.

In other recent cases, human subjects in flawed research studies have died prematurely, and subsequent questions were raised about whether the doctors involved gave advice biased by their financial interests. But experts say they are unaware of any instance when a university president has held a large, personal financial stake in a drug being tested at his institution.

Mendelsohn, in an interview, acknowledged the potential for conflict between his roles as M.D. Anderson president and a board member of ImClone, but he said he had tried to balance them carefully.

He emphasized that he had played no direct role in caring for patients as they were deciding whether to take Erbitux. And he said his institution had enrolled patients in tests of competing drugs.

Mendelsohn said it was on his initiative, last year, that M.D. Anderson decided to toughen its policies on disclosure so that patients would be formally told of such a conflict. Mendelsohn said he was moved to act by public concern stemming from the cases elsewhere, including a situation involving a young man's death at the University of Pennsylvania.

"I'm not sure it's necessary even today," Mendelsohn said. "But I think you move with the times. I don't want to take any chances that a patient will feel they've been deceived at M.D. Anderson." A June 30 article about the president of the M.D. Anderson Cancer Center and his financial interest in a drug being tested there mentioned a Seattle Times report about drug testing at the Fred Hutchinson Cancer Research Center. The story said that several Hutchinson doctors "had a financial stake in the outcome" of that research. A senior official at Hutchinson denies that the doctors had a financial interest, saying they had "foreclosed any possibility of commercializing the results of these trials by publishing their research in professional journals rather than seeking patent protection." The Seattle Times has quoted patent attorneys as saying the doctors could have won patent protection later and thereby profited from the research.

Advocates for improved research ethics tend to think, by contrast, that disclosure in such cases is the bare minimum needed to protect patients from harm. Some go farther, saying that conflicts of interest in medical research should be prohibited.

"What's happening is a lot of talk about 'managing' conflicts of interest," in part by disclosing them to patients, "and not prohibiting them," said Marcia Angell, a Harvard University lecturer who is a former editor of the New England Journal of Medicine and a leading voice on the issue. "I think disclosure is better than nothing, absolutely. But there should be a flat-out ban."

One of the first doctors to work on Erbitux at M.D. Anderson was an oncologist named Roman Perez-Soler. He has left the hospital for unrelated reasons and is chief of medical oncology at Albert Einstein College of Medicine in New York. His name has appeared with **Mendelsohn's** in two scientific reports about Erbitux.

In an interview, Perez-Soler said he believed **Mendelsohn** had conducted himself honorably in the Erbitux situation, but could nonetheless have handled it better, perhaps by emphasizing to doctors involved that there would be no repercussions if they declined to test the drug or reported negative findings about it.

Perez-Soler stressed that he knew of no specific misconduct in the Erbitux trials, but he said the results of any medical test conducted under such conditions must be viewed cautiously, since the financial interests involved would likely translate into pressure on faculty members to produce favorable results.

When he was asked to get involved in testing the president's drug, "I knew right away this was dangerous territory," Perez-Soler said. "You need a promotion. You need a salary increase. You need another lab. It distorts the normal conduct of things, because you go all the way to try to please the boss."

Perez-Soler said he believed that doctors, and even university presidents, must be allowed to have a financial stake in drugs they develop, but that careful ethical rules need to be worked out to insulate faculty members from pressure and ensure the integrity of research.

A doctor still working for **Mendelsohn** said he had felt no undue pressure in the case of Erbitux.

James Abbruzzese, chairman of gastrointestinal oncology at M.D. Anderson, tested the drug against pancreatic cancer and reported moderately favorable results, but then turned down a larger study in colon cancer because he didn't like the way **ImClone** planned to conduct the tests. **ImClone** executives brought the matter to **Mendelsohn's** attention, but **Mendelsohn** said he declined to intervene, and Abbruzzese said he felt no pressure to reverse his decision.

"Really, Dr. **Mendelsohn** was not involved in any of this discussion," Abbruzzese said. "If I had wanted to walk away from both of these studies, I don't think there would have been any issue raised with him."

As evidence of his even-handedness, **Mendelsohn** noted that his institution had enrolled more than 300 patients in tests of Iressa, a drug sponsored by another company that is the main potential competitor of Erbitux. **Mendelsohn** has no financial stake in that drug.

There's continuing controversy among doctors and investors about just how good a drug Erbitux is. The tests at M.D. Anderson found results similar to those at other institutions, namely that Erbitux is mildly effective.

The plunge in **ImClone** shares came after the FDA raised questions about tests led by another institution, the Memorial Sloan-Kettering Cancer Center, asking if they were skewed in a way that overestimated the benefits of Erbitux. **ImClone** has acknowledged to Congress that it could have done a better job managing the tests but said it still believes the drug works for some patients.

The situation involving Erbitux is the latest chapter in a 20-year effort to develop a new type of cancer therapy.

Work in the late 1970s and early 1980s had suggested that many cancers proliferate in response to specific proteins called growth factors. Working at the University of California at San Diego, a young John **Mendelsohn** and colleague Gordon Sato wondered what would happen if one of the most important, the epidermal growth factor, were blocked by a drug.

With help from the National Cancer Institute, Mendelsohn and Sato devised a drug they thought might work. Other companies, picking up on their theory, did the same, and through many ups and downs, these drugs in recent years have entered the advanced stages of human testing.

Eli Lilly & Co., the drug giant, was the commercial sponsor of the Mendelsohn drug for a while but dropped it. A frustrated Mendelsohn eventually persuaded a small New York company, ImClone Systems, to pick up the project.

Mendelsohn's career flourished in the meantime as he took successive positions at the nation's two most prestigious cancer centers. He worked as chairman of the department of medicine at Memorial Sloan-Kettering, in New York, then left in 1996 to take the top job at M.D. Anderson.

That huge Texas institution, named for a Houston cotton broker, is a unit of the state university system that is of critical significance in the nation's struggle against cancer.

Every year it enrolls some 1 percent of all cancer patients, perpetually rivaling Sloan-Kettering as the largest center. It offers the sickest patients access to experimental treatments that represent their last hope, and it often defines new approaches to cancer care that spread across the country.

At the time Mendelsohn took over as president, he was an adviser to ImClone and held a financial stake in the success of the drug. He had not yet joined the ImClone board.

At M.D. Anderson, as at some other institutions, outside financial ties were once prohibited. But by the mid-1990s these strictures were being lifted across the country, including at M.D. Anderson, under pressure from faculty members who felt they should be able to benefit from valuable discoveries they made.

Mendelsohn said he knew from the outset he would need to keep his financial interests from coloring his judgment as president. At the same time, he said, he felt tests of the drug could go forward if he kept a proper distance. ImClone's representatives "negotiated directly with our contracts office and the investigators involved" to mount tests, Mendelsohn said. M.D. Anderson had no guidelines requiring patient notification of a conflict involving top officers.

It is clear some patients knew of Mendelsohn's role in inventing the drug -- they tracked him down to plead for access to it, and were referred to other M.D. Anderson doctors. But in the formal document patients signed consenting to experimental treatment, they were not informed of Mendelsohn's financial stake.

The theoretical risks in this situation are numerous, according to safety advocates. With hidden financial interests at stake, patients might be pushed toward particular experimental drugs so as to complete those trials quickly, rather than given objective options. "Human research subjects are in short supply, and what the sponsors want is to get as many enrolled as rapidly as possible," Angell said.

Additionally, according to a report by the General Accounting Office, the investigative arm of Congress, the financial interests might create an incentive to play down the risks of a particular drug. And they might also create a motive for doctors with stock options on the line to ignore side effects or massage test results.

"There's a temptation, in these circumstances, to under-report toxicity and over-report the activity of the drug," Perez-Soler said.

Serious questions about conflict of interest were raised in two recent cases of national import. Jesse Gelsinger, 18, of Tucson, died at the University of Pennsylvania in 1999 after volunteering to test an experimental treatment designed to help babies who shared his genetic ailment, ornithine transcarbamylase deficiency.

James Wilson, director of the center where Gelsinger died, had a direct financial interest. It later emerged that Wilson and other doctors had ignored serious danger signals when they proceeded with the test that killed Gelsinger.

Unlike in the M.D. Anderson instance, some of the financial interests were disclosed to the Gelsinger family. But still, serious questions were raised after Gelsinger's death about whether he got unbiased medical advice, and the University of Pennsylvania settled with his family for several million dollars. "Looking back, I can see that I was very naive to have been as trusting as I was," his father, Paul Gelsinger, told Congress.

Similar issues are being debated in Seattle, where the Seattle Times recently questioned tests that the newspaper alleged had killed patients prematurely at the Fred Hutchinson Cancer Research Center. Some of the doctors who designed those tests had a financial stake in the outcome.

Mendelsohn, in an interview at his office in Houston, said he had been aware for many years that financial interests can cloud a doctor's judgment. That's why he recently instituted a policy at M.D. Anderson, he said, that no doctor directly involved in clinical care of a patient can have a financial stake in an experimental drug being offered to that patient.

Policies like that have been spreading nationwide in light of the Gelsinger disaster, but they are far from universal.

Just as the academic world is groping toward policies for individual doctors, a new type of conflict -- the type that Mendelsohn exemplifies -- has gained increasing attention. This is "institutional conflict of interest," or a circumstance in which an institution or one of its senior officers holds a financial interest in a drug that institution plans to test.

More and more, universities are filing patents on key discoveries and licensing those to drug companies, giving the university a potentially lucrative stake. And, as the Mendelsohn case shows, discoveries researchers make early in their careers can create conflicts after they have advanced to the top ranks.

Professional bodies have only lately begun studying the issue. "On the institutional side, we're way, way farther back in our work nationally," said David Skorton, a vice president at the University of Iowa who is active in the issue.

The GAO has complained repeatedly that the federal government has been slow to improve standards. Such work is underway, said Greg Koski, director of human research protection in the Department of Health and Human Services, but no national consensus has emerged on exactly how far to go in restricting institutional conflicts.

"I don't think anyone at this point is entirely convinced that they have all the answers," Koski said.

After he had been at M.D. Anderson for two years, Mendelsohn was asked to join ImClone's board, deepening his financial involvement.

He sought legal advice from M.D. Anderson's attorney, who approved the arrangement based in part on Mendelsohn's claim that he had kept his two roles separate. "I understand that you have strictly avoided any participation in the research being conducted at the institution sponsored by ImClone," attorney Dan Fontaine wrote in a Feb. 6, 1998, memorandum.

There are questions, however, about whether Mendelsohn continued to do so after joining the ImClone board. He has appeared as an author on 11 scientific papers and abstracts reporting research on Erbitux that were published after the date of the memo, and four of those involved research on human subjects that was conducted partly or wholly at M.D. Anderson.

Mendelsohn said the papers in question reported studies that he helped design before moving from Sloan-Kettering to the presidency of M.D. Anderson. He said the work took considerable time to complete and write up for publication,

which he said explains why some of it appeared as late as 2001. He said he has had no recent involvement in the research and did not feel he had violated the commitment implicit in the Fontaine memo.

"I just have gotten out of it," Mendelsohn said.

However modest the Erbitux results, as the drug came up for FDA consideration in 2001, glowing articles appeared about it in Business Week and other publications. ImClone shares rose 94 percent that year to peak at $73.83 in December.

In the midst of the optimism, ImClone cut the biggest deal of its type ever with drug giant Bristol-Myers Squibb Co., which agreed to invest more than $2 billion for a stake in ImClone and some rights to the drug. One beneficiary was Mendelsohn, who earned $6.3 million when he sold a stake to Bristol last fall in an offer open to all ImClone shareholders.

But then disaster struck. ImClone announced on Dec. 28 that the FDA was throwing out its application for early approval, citing flawed tests. Subsequent disclosures raised serious questions about whether company insiders, including board members, knew as far back as the time of the Bristol tender offer, in October, that bad news was coming. Unlike some company insiders, Mendelsohn reported no stock sales in December, and he retains a significant stake in ImClone.

ImClone shares have plummeted 88 percent, closing Friday at $8.69. Extensive investigations are underway in Washington and New York, and a slew of corporate executives and FDA administrators testified about the matter on Capitol Hill on June 13.

Samuel Waksal, who was chief executive of ImClone during the events of December, has been arrested on charges that he tipped family members to sell their ImClone shares just ahead of the bad news. A related investigation is focusing on whether he, or anyone else, tipped Stewart to sell her 4,000 shares in the nick of time.

Mendelsohn said he had never sold stock based on inside information, and he stressed that he had always been up front about his financial stake. Only after Erbitux had become embroiled in controversy, however, did most faculty members of the M.D. Anderson Cancer Center receive word that from now on, they would have to inform patients in writing of Mendelsohn's special connection to Erbitux.

Now the institution is wrestling with an additional issue: Even when patients are told of a financial interest that might influence the medical advice they get, they don't necessarily understand that what is being disclosed to them is an extra risk to weigh.

"When they find out their doctor is the person that invented something, they think that's just sliced bread," said Leonard Zwelling, Mendelsohn's vice president for research administration. "They say, 'I've come to the right place. This is the best I could hope for.' "

CORRECTION-DATE: July 25, 2000July 25, 2002

CORRECTION: A June 30 article about the president of the M.D. Anderson Cancer Center and his financial interest in a drug being tested there mentioned a Seattle Times report about drug testing at the Fred Hutchinson Cancer Research Center. The story said that several Hutchinson doctors "had a financial stake in the outcome" of that research. A senior official at Hutchinson denies that the doctors had a financial interest, saying they had "foreclosed any possibility of commercializing the results of these trials by publishing their research in professional journals rather than seeking patent protection." The Seattle Times has quoted patent attorneys as saying the doctors could have won patent protection later and thereby profited from the research.

LOAD-DATE: June 30, 2002

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[The Atlanta Journal-Constitution: 7/5/02]

Patients a low priority for drug industry leaders

By FRED SANTINO

Fred Santino is a faculty member at Babson College in Wellesley, Mass.

After the Enron, Tyco and Andersen fiascos, it seemed that the "Business Ethics Hall of Shame" was full, but the newest addition, ImClone, just might be the worst.

ImClone's ex-CEO, Sam Waksal, was recently arrested by the FBI for alleged insider trading. Sam and his brother Harlan allegedly knew that ImClone's Erbitux (C-225) was about to be disapproved by the Food and Drug Administration, and tipped off family members and friends to sell shares to profit before prices plummeted.

Ethics lapses in the drug industry are especially disturbing since numerous cancer patients depend on people such as Waksal for life. If drug industry leaders cheat, people can die – such as my wife, Ruth-Ann.

Ruth-Ann, 51, the mother of two teenage sons, had been fighting colorectal cancer for more than two years. When standard treatments didn't work, her doctors advised her to seek the experimental C-225, produced by ImClone. ImClone's Web site showed that C-225 trials were open and ongoing, and its telephone "hotline" kept promising that new trials would be available "in a few weeks."

Ruth-Ann wrote several desperate letters and faxes, but ImClone management repeatedly chose to ignore her. If ImClone had given her a timely "no," Ruth-Ann would have entered a lesser-known, but promising treatment at Memorial Sloan-Kettering Cancer Center, New York. Ruth-Ann also learned that another patient at her own cancer center had succeeded in getting C-225 from ImClone.

CBS' "60 Minutes" began to investigate the arbitrary and unfair distribution of C-225 and interviewed Ruth-Ann for the story. Before the show aired, Ruth-Ann's condition continued to worsen. As I sat by her bedside, the phone rang and one of my sons answered it.

"Dad, it's ImClone!" he cried out. "Maybe they're going to give Mom the drug." As I took the phone, it was Dr. Harlan Waksal himself, complaining that, "You're being unfair to ImClone by going on '60 Minutes'!"

Certainly, I couldn't stop the show and didn't want to. Upon my furious reaction, both my sons immediately broke down. "Dad . . . does that mean Mom isn't going to get better?" Waksal never asked me how Ruth-Ann was doing, even though

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any human being would realize that her condition must be desperate after two years of cancer. She died two days later.

A month later, at a congressional hearing, Waksal still didn't adequately explain ImClone's arbitrary C-225 distribution and his failure to respond to my wife, but it gave me a chance to express my anger in person and on national news. Our loss was difficult enough, but ImClone's behavior made her death even harder to deal with.

Recently, the FDA rejected approval of Erbitux with concern over the way C-225 was tested. This news, combined with the charges of insider trading, makes one wonder if ImClone's leadership really cared about approval. Why care about product approval if you can profit from stock prices? Yet if the drug really works, the FDA action is a setback for thousands of cancer patients.

Was ImClone's business priority cancer treatment or stock profiteering? When congressional investigators asked Waksal that question recently, he refused to answer.

This sad story is further proof that we must demand higher ethical standards from our business leaders. If ImClone had focused more on its product, the company might not be in such trouble, criminal investigations might not be ongoing, and many cancer sufferers -- including my wife, Ruth-Ann -- might still be alive.

Fred Santino is a faculty member at Babson College in Wellesley, Mass.

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UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

UNITED STATES OF AMERICA	:	
- v. -	:	INDICTMENT
SAMUEL WAKSAL,	:	02 Cr.
Defendant.	:	

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COUNT ONE

(Conspiracy to Commit Fraud in Connection with the Purchase and Sale of Securities: Samuel Waksal and Tippee No. 1)

The Grand Jury charges:

Background

1. At all times relevant to this Indictment, ImClone Systems Incorporated ("ImClone") was a corporation organized under the laws of the State of Delaware with its principal place of business in New York, New York. ImClone was engaged in the business of developing biologic medicines, including the development of Erbitux, a biologic treatment for irinotecan-refractory colorectal cancer. ImClone publicly described Erbitux as its lead product candidate. At all times relevant to this Indictment, ImClone's common stock was listed on the NASDAQ National Market System, an electronic securities market system administered by the National Association of Securities Dealers, under the symbol "IMCL."

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2. Until on or about May 22, 2002, when he resigned, SAMUEL WAKSAL, the defendant, was president, chief executive officer, and a director of ImClone.

Samuel Waksal's Financial Condition

3. As of on or about December 26, 2001, SAMUEL WAKSAL, the defendant, had more than approximately $75 million in indebtedness, over $50 million of which was "margin debt" secured by his shares of ImClone stock. At that time, WAKSAL had to pay more than approximately $800,000 each month to service his indebtedness. As WAKSAL well knew, in the event that the market price of ImClone stock declined substantially, WAKSAL's ImClone stock that secured his "margin debt" would likely be sold and, as a result, his net worth would decrease dramatically.

ImClone's Policies on Insider Trading

4. At all times relevant to this Indictment, ImClone distributed memoranda advising its officers and employees, including SAMUEL WAKSAL, the defendant, of their responsibilities under the federal securities laws. In or about April 2001, as well as in preceding years, ImClone distributed a memorandum advising employees of its insider trading policy, which stated in part:

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U.S. securities laws give the Company, its directors, officers and other employees, among others, the responsibility to ensure that information about the Company is not used unlawfully in the purchase and sale of securities.
All directors, officers and other employees should pay close attention to the laws against trading on "inside" information. These laws are based upon the belief that all persons trading in a company's securities should have equal access to all "material" information about the company. For example, if an employee of a company knows material, non-public information, that employee is prohibited from buying or selling stock in the company until the information has been disclosed to the public. That is because the employee knows information that will very likely cause the stock price to change, and it would be unfair for the employee to have an advantage that the rest of the investing public does not have. In fact, it is more than unfair, it is fraudulent and illegal.
. . .

The general rule is that it is a violation of the federal securities laws for any person to buy or sell securities if he or she is in possession of material inside information. Information is "material" if it could affect a person's decision whether to buy, sell or hold the securities. It is "inside" information if it has not been publicly disclosed. Furthermore, it is illegal for any person in possession of material inside information to provide other people with such information or to recommend that they buy or sell the securities ("tipping"). In that case, they may both be held liable. . . .

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5. At all times relevant to this Indictment, ImClone also established so-called "Blackout Periods" during which its officers and employees were prohibited from engaging in any transactions in ImClone common stock. The Blackout Period was described to ImClone personnel in a memorandum. The memorandum further instructed directors and officers not to execute any transaction in ImClone stock during a Blackout Period without first receiving authorization from ImClone's Office of the General Counsel.

The Insider Trading Scheme

SAMUEL WAKSAL's Acquisition of Inside Information

6. On or about October 31, 2001, ImClone submitted to the United States Food and Drug Administration (the "FDA") a Biologics Licensing Application ("BLA") for approval of Erbitux (the "Erbitux BLA"). Pursuant to FDA regulations, within 60 days following the submission of a BLA, the FDA must decide whether the BLA is administratively and scientifically complete to be accepted for FDA review. Only if a BLA is accepted for filing does the FDA review the application to determine whether the proposed treatment will be approved.

7. Because ImClone expected decisions from the FDA on whether the Erbitux BLA would be accepted for filing and whether the Erbitux BLA would be granted expedited review, on

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December 21, 2001, ImClone's Office of the General Counsel distributed an email to all ImClone employees placing into effect a "company-wide blackout in trading in ImClone stock." The email stated that "the FDA is required to tell us by the end of next week whether the filing of our BLA for Erbitux has been accepted and whether the file will be granted expedited review," and "[g]iven the importance of this news, we believe employees should not trade in ImClone stock until we receive definitive information from the FDA and a press release is issued."

8. On December 25, 2001, ImClone's then executive vice-president and chief operating officer was informed that a source within the FDA had stated that it was almost certain that on December 28, 2001, ImClone would receive from the FDA a "Refusal to File Letter," by which the FDA would advise ImClone that it had refused to accept the Erbitux BLA for filing.

9. On or about December 26, 2001, SAMUEL WAKSAL, the defendant, learned of the report that a source within the FDA had stated that ImClone was expected to receive a Refusal to File Letter on December 28, 2001. As of December 26, 2001, this information about the FDA's anticipated decision on the Erbitux BLA was material non-public information. Moreover, as WAKSAL well knew, any subsequent public announcement that the FDA had issued a "Refusal to File Letter" or had otherwise declined to

proceed with reviewing and approving the Erbitux BLA would likely have an adverse impact on the market price for ImClone's stock.

The Unlawful Trading

10. As an officer and director of ImClone, SAMUEL WAKSAL, the defendant, owed fiduciary and other duties to ImClone and its shareholders to abstain from trading in ImClone common stock while in possession of material non-public information concerning ImClone's Erbitux BLA. SAMUEL WAKSAL owed further duties to ImClone and its shareholders to protect the confidentiality of such material non-public information, and to abstain from "tipping" such material non-public information to others. In breach of those duties and for his own personal benefit and the benefit of other persons with whom he had a close personal relationship, SAMUEL WAKSAL disclosed confidential, material non-public information that he had misappropriated and stolen from ImClone about the FDA's anticipated decision. WAKSAL disclosed this information, in substance and in part, to, among others known and unknown, a co-conspirator not named as a defendant herein ("Tippee No. 1") and recommended that Tippee No. 1 sell ImClone stock. Tippee No. 1, in turn, sold ImClone common stock while knowing that the information was confidential, material and non-public and had

been disclosed to Tippee No. 1 in breach of SAMUEL WAKSAL's duties to ImClone and ImClone's shareholders.

11. In or about the late evening of December 26, 2001, SAMUEL WAKSAL, the defendant, contacted Tippee No. 1 and communicated to Tippee No. 1 that Tippee No. 1 should sell ImClone common stock. The following day, December 27, 2001, by approximately 9:41 a.m. (EST), Tippee No. 1 placed orders to sell approximately 111,336 shares of ImClone common stock then worth approximately $6,852,255. On or about December 28, 2001, at approximately 9:07 a.m. (EST), Tippee No. 1 placed an order to sell an additional approximately 25,000 shares of ImClone common stock worth approximately $1,429,750.

Public Announcement of the FDA Decision

12. On or about December 28, 2001, at approximately 2:55 p.m. (EST), the FDA transmitted to ImClone via facsimile a letter stating that the FDA had refused to accept the Erbitux BLA for filing. After the close of business on December 28, 2001, ImClone issued a press release announcing that the FDA had refused to accept the Erbitux BLA for filing (the "RTF Press Release").

13. On December 28, 2001, prior to the issuance of the RTF Press Release, the closing price of ImClone stock was $55.25. On December 31, 2001, the first day that ImClone stock

traded after the issuance of the RTF Press Release, the price of ImClone stock closed at $46.46, representing a decline of approximately 16%.

14. By selling a total of 136,336 shares of ImClone stock in the two days prior to ImClone's public announcement of the FDA's refusal to accept for filing the Erbitux BLA, Tippee No. 1 avoided losses of approximately $1.9 million. On or about January 18, 2002, Tippee No. 1 wire transferred approximately $2,850,000 from his account at Roth Capital Partners, LLC, to an account in the name of SAMUEL WAKSAL, the defendant, at UBS Paine Webber.

The Conspiracy

15. From on or about December 26, 2001, up to and including on or about January 18, 2002, in the Southern District of New York and elsewhere, SAMUEL WAKSAL, the defendant, and Tippee No. 1 unlawfully, willfully, and knowingly did combine, conspire, confederate and agree together and with each other to commit offenses against the United States, to wit, to commit securities fraud in violation of Title 15, United States Code, Sections 78j(b) and 78ff, and Title 17, Code of Federal Regulations, Section 240.10b-5, and to commit wire fraud in violation of Title 18, United States Code, Section 1343.

Objects of the Conspiracy

Securities Fraud

16. It was a part and an object of the conspiracy that SAMUEL WAKSAL, the defendant, and Tippee No. 1 unlawfully, willfully and knowingly, directly and indirectly, by use of the means and instrumentalities of interstate commerce, the mails and the facilities of national securities exchanges, did use and employ manipulative and deceptive devices and contrivances, in violation of Title 17, Code of Federal Regulations, Section 240.10b-5, by (a) employing devices, schemes and artifices to defraud; (b) making untrue statements of material facts and omitting to state material facts necessary in order to make the statements made, in the light of the circumstances under which they were made, not misleading; and (c) engaging in acts, practices and courses of business which operated and would and did operate as a fraud and deceit upon ImClone and its shareholders, and other persons and entities, in connection with the purchase and sale of ImClone securities, in violation of Title 15, United States Code, Sections 78j(b) and 78ff, and Title 17, Code of Federal Regulations, Section 240.10b-5.

Wire Fraud

17. It was further a part and an object of the conspiracy that SAMUEL WAKSAL, the defendant, and Tippee No. 1, having devised and intending to devise a scheme and artifice to

defraud, and for obtaining money and property by means of false and fraudulent pretenses, representations and promises, unlawfully, willfully and knowingly would and did transmit and cause to be transmitted by means of wire communication in interstate and foreign commerce, writings, signs, signals, pictures and sounds for the purpose of executing such scheme and artifice, in violation of Section 1343 of Title 18, United States Code.

Means and Methods of the Conspiracy

18. Among the means and methods by which SAMUEL WAKSAL, the defendant, and Tippee No. 1 would and did carry out the conspiracy were the following:

a. SAMUEL WAKSAL misappropriated and stole material non-public information concerning the status of the Erbitux BLA and the FDA's pending actions on that application, in violation of (i) the fiduciary and other duties of trust and confidence that SAMUEL WAKSAL owed to ImClone and its shareholders; and (ii) ImClone's written policies regarding the use and safekeeping of confidential and proprietary information.

b. For his own benefit and the benefit of Tippee No. 1, with whom SAMUEL WAKSAL had a close personal relationship, SAMUEL WAKSAL disclosed to Tippee No. 1 material

non-public information that he had misappropriated and stolen from ImClone and its shareholders with the understanding that Tippee No. 1 would sell shares of ImClone common stock and thereby avoid substantial losses.

c. Tippee No. 1 sold shares of ImClone common stock on the basis of information and recommendations provided by SAMUEL WAKSAL, thereby avoiding substantial losses.

Overt Acts

19. In furtherance of the conspiracy and to effect the illegal objects thereof, the following overt acts, among others, were committed in the Southern District of New York and elsewhere:

a. In or about the late evening of December 26, 2001, SAMUEL WAKSAL, the defendant, who was in New York, New York, spoke by telephone with Tippee No. 1, who was in another state.

b. On or about December 27, 2001, Tippee No. 1 spoke by telephone with a representative of Roth Capital Partners, LLC, during which Tippee No. 1 placed an order to sell 50,000 shares of ImClone common stock.

c. On or about December 27, 2001, Tippee No. 1 spoke by telephone with a representative of McDonald

Investments, Inc., during which Tippee No. 1 placed an order to sell 50,000 shares of ImClone common stock.

d. On or about December 27, 2001, Tippee No. 1 spoke by telephone with a representative of Banc of America Securities LLC, during which Tippee No. 1 placed an order to sell 10,000 shares of ImClone common stock.

e. On or about December 27, 2001, Tippee No. 1 spoke by telephone with a representative of Prudential Securities Incorporated, Inc., during which Tippee No. 1 placed an order to sell 1,336 shares of ImClone common stock.

f. On or about December 28, 2001, Tippee No. 1 spoke by telephone with a representative of Roth Capital Partners, LLC, during which Tippee No. 1 placed an order to sell 25,000 shares of ImClone common stock.

(Title 18, United States Code, Section 371).

COUNT TWO

(Conspiracy to Commit Fraud in Connection with the Purchase and Sale of Securities: Samuel Waksal and Tippee No. 2)

The Grand Jury further charges:

20. The allegations of paragraphs 1 through 14 and 18 through 19 are repeated and realleged as though fully set forth herein.

The Unlawful Trading

Sales of ImClone Stock By Tippee No. 2

21. In breach of his duties to ImClone and its shareholders to abstain from trading in ImClone common stock while in possession of material non-public information concerning ImClone's Erbitux BLA to ImClone and its shareholders, to protect the confidentiality of such material non-public information, and to abstain from "tipping" such material non-public information to others, and for his own personal benefit and the benefit of other persons with whom he had a close personal relationship, SAMUEL WAKSAL disclosed material non-public information, in substance and in part, to, among others known and unknown, a co-conspirator not named as a defendant herein ("Tippee No. 2") and recommended that Tippee No. 2 sell ImClone stock. Tippee No. 2, in turn, sold ImClone common stock while knowing that the information was confidential, material and non-public and had been disclosed to Tippee No. 2 in breach of SAMUEL WAKSAL's duties to ImClone and ImClone's shareholders.

22. In or about the early morning of December 27, 2001, SAMUEL WAKSAL, the defendant, contacted Tippee No. 2 and communicated to Tippee No. 2 that Tippee No. 2 should sell ImClone common stock. On or about December 27, 2001, at approximately 9:01 a.m. (EST), Tippee No. 2 placed an order to sell all of Tippee No. 2's securities holdings, consisting of approximately 39,472 shares of ImClone common stock worth approximately $2,472,837.

23. By selling 39,472 shares of ImClone stock two days prior to ImClone's public announcement of the FDA's refusal to accept for filing the Erbitux BLA, Tippee No. 2 avoided losses of approximately $630,000.

Attempted Sale of ImClone Stock Transferred to Tippee No. 2

24. In or about the morning of December 27, 2001, SAMUEL WAKSAL, the defendant, directed Merrill Lynch & Co., Inc. ("Merrill Lynch") to transfer into an account at Merrill Lynch in the name of Tippee No. 2 all of the ImClone common stock that SAMUEL WAKSAL held at Merrill Lynch, consisting of approximately 79,797 shares then valued at approximately $4.9 million (the "79,797 Shares"). SAMUEL WAKSAL's written direction to Merrill Lynch stated that the transfer request was "URGENT - IMMEDIATE ACTION REQUIRED" and that it was "imperative" that the transfer take place during the morning of December 27, 2001. Subsequent

to the transfer of the 79,797 Shares, SAMUEL WAKSAL directed his accountant to seek to have the 79,797 Shares sold. Merrill Lynch refused to sell the 79,797 Shares absent approval from ImClone's Office of the General Counsel because the shares had originally been owned by SAMUEL WAKSAL and were subject to restrictions on trading.

25. On or about December 28, 2001, after SAMUEL WAKSAL, the defendant, was informed that Merrill Lynch had refused to sell the 79,797 Shares, WAKSAL directed his accountant to arrange for the 79,797 Shares to be transferred to Banc of America Securities LLC. On December 28, 2001, at approximately 2:12 p.m., SAMUEL WAKSAL's accountant informed SAMUEL WAKSAL by email that "B[anc] of A[merica] consider[s] [Tippee No. 2] an affiliate of ImClone and cannot sell the shares absent company approval."

The Conspiracy

26. From on or about December 27, 2001, up to and including on or about December 28, 2001, in the Southern District of New York and elsewhere, SAMUEL WAKSAL, the defendant, and Tippee No. 2 unlawfully, willfully, and knowingly did combine, conspire, confederate and agree together and with each other to commit offenses against the United States, to wit, to commit securities fraud in violation of Title 15, United

States Code, Sections 78j(b) and 78ff, and Title 17, Code of Federal Regulations, Section 240.10b-5, and to commit wire fraud in violation of Title 18, United States Code, Section 1343.

Objects of the Conspiracy

Securities Fraud

27. It was a part and an object of the conspiracy that SAMUEL WAKSAL, the defendant, and Tippee No. 2 unlawfully, willfully and knowingly, directly and indirectly, by use of the means and instrumentalities of interstate commerce, the mails and the facilities of national securities exchanges, did use and employ manipulative and deceptive devices and contrivances, in violation of Title 17, Code of Federal Regulations, Section 240.10b-5, by (a) employing devices, schemes and artifices to defraud; (b) making untrue statements of material facts and omitting to state material facts necessary in order to make the statements made, in the light of the circumstances under which they were made, not misleading; and (c) engaging in acts, practices and courses of business which operated and would and did operate as a fraud and deceit upon ImClone and its shareholders, and other persons and entities, in connection with the purchase and sale of ImClone securities, in violation of Title 15, United States Code, Sections 78j(b) and 78ff, and Title 17, Code of Federal Regulations, Section 240.10b-5.

Wire Fraud

28. It was further a part and an object of the conspiracy that SAMUEL WAKSAL, the defendant, and Tippee No. 2, having devised and intending to devise a scheme and artifice to defraud, and for obtaining money and property by means of false and fraudulent pretenses, representations and promises, unlawfully, willfully and knowingly would and did transmit and cause to be transmitted by means of wire communication in interstate and foreign commerce, writings, signs, signals, pictures and sounds for the purpose of executing such scheme and artifice, in violation of Title 18, United States Code, Section 1343.

Means and Methods of the Conspiracy

29. Among the means and methods by which SAMUEL WAKSAL, the defendant, and Tippee No. 2 would and did carry out the conspiracy were the following:

e. SAMUEL WAKSAL, the defendant, misappropriated and stole material non-public information concerning the status of the Erbitux BLA and the FDA's pending actions on that application, in violation of (i) the fiduciary and other duties of trust and confidence that SAMUEL WAKSAL owed to ImClone and its shareholders; and (ii) ImClone's written

policies regarding the use and safekeeping of confidential and proprietary client information.

f. For his benefit and the benefit of Tippee No. 2, with whom SAMUEL WAKSAL had a close personal relationship, SAMUEL WAKSAL disclosed to Tippee No. 2 material non-public information that he had misappropriated and stolen from ImClone and its shareholders with the understanding that Tippee No. 2 would sell shares of ImClone common stock and thereby avoid substantial losses.

g. Tippee No. 2 sold shares of ImClone common stock on the basis of information and recommendations provided by SAMUEL WAKSAL, thereby avoiding substantial losses.

Overt Acts

30. In furtherance of the conspiracy and to effect the unlawful objects thereof, the following overt acts, among others, were committed in the Southern District of New York and elsewhere:

a. On or about December 27, 2001, SAMUEL WAKSAL, the defendant, who was in New York, New York, spoke by telephone with Tippee No. 2, who was in another state.

b. On or about December 27, 2001, Tippee No. 2, who was in another state, spoke by telephone with a representative of Merrill Lynch in New York, New York, during

which Tippee No. 2 placed an order to sell 39,472 shares of ImClone common stock.

(Title 18, United States Code, Section 371).

COUNTS THREE THROUGH NINE

(Securities Fraud)

The Grand Jury further charges:

31. The allegations of paragraphs 1 through 14, 18 through 19, 21 through 25, and 29 through 30 are repeated and realleged as though fully set forth herein.

32. On or about the following dates, in the Southern District of New York and elsewhere, SAMUEL WAKSAL, the defendant, unlawfully, willfully and knowingly, directly and indirectly, by use of the means and instrumentalities of interstate commerce, the mails and the facilities of national securities exchanges, did use and employ manipulative and deceptive devices and contrivances, in violation of Title 17, Code of Federal Regulations, Section 240.10b-5, by (a) employing devices, schemes and artifices to defraud; (b) making untrue statements of material facts and omitting to state material facts necessary in order to make the statements made, in the light of the circumstances under which they were made, not misleading; and (c) engaging in acts, practices and courses of business which operated and would and did operate as a fraud and

deceit upon ImClone and its shareholders, and other persons and entities, in connection with the following sales of ImClone stock:

COUNT	DATE	ACT
THREE	December 27, 2001	Sale of 39,472 shares of ImClone common stock from an account at Merrill Lynch held in the name of Tippee No. 2
FOUR	December 27, 2001	Attempted sale of 79,797 shares of ImClone common stock transferred to an account at Merrill Lynch held in the name of Tippee No. 2
FIVE	December 27, 2001	Sale of 50,000 shares of ImClone common stock from an account at Roth Capital Partners, LLC, held in the name of Tippee No. 1
SIX	December 27, 2001	Sale of 50,000 shares of ImClone common stock from an account at McDonald Investments, Inc. held in the name of Tippee No. 1
SEVEN	December 27, 2001	Sale of 10,000 shares of ImClone common stock from an account at Banc of America Securities held in the name of Tippee No. 1
EIGHT	December 27, 2001	Sale of 1,336 shares of ImClone common stock from an account at Prudential Securities Incorporated held in the name of another individual
NINE	December 28, 2001	Sale of 25,000 shares of ImClone common stock from an account at Roth Capital Partners, LLC, held in the name of Tippee No. 1

(Title 15, United States Code, Sections 78j(b) and 78ff;
Title 17, Code of Federal Regulations, Section 240.10b-5;
and Title 18, United States Code, Section 2.)

COUNT TEN

(Conspiracy to Obstruct Justice and Commit Perjury)

The Grand Jury further charges:

33. The allegations of paragraphs 1 through 14, 18 through 19, 21 through 25, and 29 through 30 are repeated and realleged as though fully set forth herein.

Introduction

34. Following the commencement of an investigation by the United States Securities and Exchange Commission (the "SEC") into the trading in ImClone stock described in Counts One through Nine above, SAMUEL WAKSAL, the defendant, agreed with Tippee No. 1 and Tippee No. 2 to obstruct the SEC's investigation by providing false and misleading information and by making false and misleading statements in testimony before the SEC.

The SEC Investigation

35. In or about January 2001, the Northeast Regional Office of the SEC commenced an investigation to determine whether SAMUEL WAKSAL, the defendant, and others had violated the federal securities laws and regulations that prohibit trading while in possession of and using material non-public information. It was material to the SEC's investigation to determine, among other things, the reasons for the trading,

transfers of stock, and attempted trading of SAMUEL WAKSAL, Tippee No. 1, and Tippee No. 2, among others.

36. On or about January 28, 2002, the SEC issued an Order Directing Private Investigations and Designating Officers to Take Testimony (the "Formal Order of Investigation").

37. During the course of its investigation, the SEC issued the following investigative subpoenas and made the following voluntary request for documents, among others:

gg. On or about January 8, 2002, prior to the SEC's issuance of the Formal Order of Investigation, the SEC made a voluntary request for production of documents to ImClone, requesting, among other things, the production of correspondence with any broker, dealer or financial institution regarding trading in ImClone securities by any ImClone insider.

hh. On or about January 30, 2002, the SEC issued a subpoena to SAMUEL WAKSAL, the defendant, directing WAKSAL to provide testimony and to produce documents relating to, among other things: (i) any securities trading and bank accounts WAKSAL controlled; (ii) any financial arrangement, agreement or transaction between WAKSAL and any other person with respect to the purchase or sale of securities or the proceeds thereof; and (iii) any wire transfers WAKSAL authorized in connection with any such arrangement, agreement or transaction.

ii. On or about January 30, 2002, the SEC issued a subpoena to Tippee No. 1, directing Tippee No. 1 to provide testimony and produce documents relating to Tippee No. 1's trading in ImClone securities, among other things.

jj. On or about January 30, 2002, the SEC issued a subpoena to Tippee No. 2, directing Tippee No. 2 to provide testimony and produce documents relating to Tippee No. 2's trading in ImClone securities, among other things.

kk. On or about March 26, 2002, and April 9, 2002, the SEC issued subpoenas to ImClone for documents relating to, among other things, any transaction in ImClone securities by any ImClone officer or director and any brokerage accounts maintained by any ImClone officer or director.

The Scheme to Obstruct Justice

38. Following the SEC's issuance of subpoenas directing SAMUEL WAKSAL, the defendant, Tippee No. 1 and Tippee No. 2 to give testimony, WAKSAL, Tippee No. 1, and Tippee No. 2 agreed to make false and misleading statements to the SEC about their communications regarding their trading in ImClone stock.

39. On April 1, 2002 and April 18, 2002, SAMUEL WAKSAL, the defendant, appeared before the SEC in New York, New York, pursuant to subpoena, and gave testimony under oath.

Among other matters, SAMUEL WAKSAL falsely testified, in substance and in part, that:

gg. SAMUEL WAKSAL did not speak with Tippee No. 1 during the night of December 26, 2001; did not instruct Tippee No. 1 to sell ImClone stock on or about December 27, 2001 or on or about December 28, 2001; and did not suggest to Tippee No. 1 that Tippee No. 1 should sell ImClone stock on or about December 27, 2001 or on or about December 28, 2001.

hh. SAMUEL WAKSAL did not speak with Tippee No. 2 from the time he heard the report of the FDA's anticipated negative decision regarding the Erbitux BLA until the night of December 27, 2001; did not instruct Tippee No. 2 to sell ImClone stock on or about December 27, 2001; and did not suggest to Tippee No. 2 that Tippee No. 2 should sell ImClone stock on or about December 27, 2001.

ii. SAMUEL WAKSAL had planned to transfer the 79,797 Shares to Tippee No. 2 a number of weeks before the transfer on or about December 27, 2001; did not believe there was any imperative associated with the transfer of the 79,797 Shares to Tippee No. 2; and did not ask to have the 79,797 Shares sold.

40. On March 18, 2002, Tippee No. 1 appeared before the SEC in Miami, Florida, pursuant to subpoena, and gave

testimony under oath. Among other matters, Tippee No. 1 falsely testified, in substance and in part, that Tippee No. 1 (a) "never had a conversation about stock with [SAMUEL WAKSAL]"; (b) "never spoke to [SAMUEL WAKSAL] about ImClone"; (c) remembered that Tippee No. 1 did not talk to SAMUEL WAKSAL on the night of December 26, 2001; and (d) did not return any of the calls SAMUEL WAKSAL placed to Tippee No. 1 during the night of December 26, 2001.

41. On March 5, 2002, Tippee No. 2 appeared before the SEC in New York, New York, pursuant to subpoena, and gave testimony under oath. Among other matters, Tippee No. 2 falsely testified, in substance and in part, that (a) prior to placing the December 27, 2001 order to sell ImClone shares, Tippee No. 2 did not speak to anyone other than the person with whom Tippee No. 2 was vacationing; (b) Tippee No. 2 did not discuss investments in any way with SAMUEL WAKSAL during Tippee No. 2's vacation to Idaho; and (c) Tippee No. 2 placed the December 27, 2001 order to sell because Tippee No. 2 needed $1.7 million to close on a two-bedroom apartment in Manhattan into which Tippee No. 2 planned to move on January 7, 2002.

42. Contrary to the testimony of SAMUEL WAKSAL, the defendant, and Tippee No. 1, telephone records show the following telephone calls between telephones associated with

SAMUEL WAKSAL and Tippee No. 1 in the late evening of December 26, 2001, just prior to the time that Tippee No. 1 placed orders to sell ImClone stock during the early morning of December 27, 2001:

Time of Call	From	To	Length of Call
9:52 p.m. (EST)	Samuel Waksal's cell phone	Tippee No. 1's home phone	2 seconds
9:56 p.m. (EST)	Samuel Waksal's cell phone	Tippee No. 1's home phone	7 seconds
Time of Call	From	To	Length of Call
10:26 p.m. (EST)	Samuel Waksal's cell phone	Tippee No. 1's home phone	22 seconds
10:41 p.m. (EST)	Tippee No. 1's home phone	Samuel Waksal's home phone	1 minute, 3 seconds
11:11 p.m. (EST)	Tippee No. 1's home phone	Samuel Waksal's home phone	42 seconds

38. Contrary to the testimony of SAMUEL WAKSAL, the defendant, and Tippee No. 2, telephone records show that early in the morning of December 27, 2001, just prior to Tippee No.2's sale of all of Tippee No. 2's ImClone stock, numerous telephone calls were placed between telephones associated with SAMUEL WAKSAL and Tippee No. 2, as follows:

Time of Call	From	To	Length of Call

6:27 a.m. (MST)	Samuel Waksal's work phone	Tippee No. 2's cell phone	Unknown
6:30 a.m. (MST)	Tippee No. 2's cell phone	Samuel Waksal's work phone	2 minutes
6:58 a.m. (MST)	Tippee No. 2's hotel phone	Samuel Waksal's work phone	2.4 minutes
7:01 a.m. (MST)	Tippee No. 2's hotel phone	Merrill Lynch	1.4 minutes
7:46 a.m. (MST)	Tippee No. 2's hotel phone	Samuel Waksal's work phone	1.3 minutes
7:49 a.m. (MST)	Tippee No. 2's hotel phone	Merrill Lynch	0.7 minutes

The Conspiracy

38. From in or about January 2002, until in or about March 2002, in the Southern District of New York and elsewhere, SAMUEL WAKSAL, the defendant, Tippee No. 1 and Tippee No. 2, unlawfully, willfully, and knowingly did combine, conspire, confederate and agree together and with each other to commit offenses against the United States, to wit, to obstruct justice, in violation of Section 1505 of Title 18, United States Code, and to commit perjury, in violation of Section 1621 of Title 18, United States Code.

Objects of the Conspiracy

Obstruction of Justice

38. It was a part and an object of the conspiracy that SAMUEL WAKSAL, the defendant, Tippee No. 1 and Tippee No. 2 unlawfully, willfully and knowingly, would and did corruptly influence, obstruct and impede, and endeavor to influence, obstruct and impede the due and proper administration of the law under which a pending proceeding was being had before a department and agency of the United States, namely, the SEC, in violation of Title 18, United States Code, Section 1505.

Perjury

39. It was further a part and an object of the conspiracy that SAMUEL WAKSAL, the defendant, Tippee No. 1 and

Tippee No. 2, having taken an oath before a competent tribunal, officer and person, in a case in which the law of the United States authorizes an oath to be administered, namely, in testimony before the SEC, would and did testify, declare, depose and certify truly, and that any written testimony, declaration, deposition and certificate by them subscribed, would be true, unlawfully, willfully, knowingly, and contrary to such oath, would and did state and subscribe material matters which they did not believe to be true, in violation of Title 18, United States Code, Section 1621.

Means and Methods of the Conspiracy

40. Among the means and methods by which SAMUEL WAKSAL, the defendant, Tippee No. 1 and Tippee No. 2 would and did carry out the conspiracy were the following:

gg. SAMUEL WAKSAL and Tippee No. 1 agreed to and did provide false and misleading testimony to the SEC about their communications the night before Tippee No. 1's sales of ImClone stock.

hh. SAMUEL WAKSAL and Tippee No. 2 agreed to and did provide false and misleading testimony to the SEC about their communications during the hours prior to Tippee No. 2's sales of ImClone stock.

Overt Acts

48. In furtherance of the conspiracy and to effect the unlawful objects thereof, the following overt acts, among others, were committed in the Southern District of New York and elsewhere:

vv. On or about March 5, 2002, in New York, New York, Tippee No. 2 gave false and misleading testimony about communications with SAMUEL WAKSAL regarding Tippee No. 2's trading in ImClone stock.

ww. On or about March 18, 2002, in Miami, Florida, Tippee No. 1 gave false and misleading testimony about communications with SAMUEL WAKSAL regarding Tippee No. 1's trading in ImClone stock.

xx. On or about April 1, 2002, in New York, New York, SAMUEL WAKSAL gave false and misleading testimony about his communications with Tippee No. 1 and Tippee No. 2 regarding Tippee No. 1's and Tippee No. 2's trading in ImClone stock.

yy. On or about April 18, 2002, in New York, New York, SAMUEL WAKSAL gave false and misleading testimony about his communications with Tippee No. 1 and Tippee No. 2 regarding Tippee No. 1's and Tippee No. 2's trading in ImClone stock.

(Title 18, United States Code, Section 371).

COUNT ELEVEN

(Perjury)

The Grand Jury further charges:

49. The allegations of paragraphs 1 through 14, 18 through 19, 21 through 25, 29 through 30, 34 through 43, and 47 through 48 are repeated and realleged as though fully set forth herein.

50. On April 1, 2002, and on April 18, 2002, in the Southern District of New York, SAMUEL WAKSAL, the defendant, having taken an oath before a competent tribunal, officer and person, in a case in which the law of the United States authorizes an oath to be administered, namely, in testimony before an officer of the United States Securities and Exchange Commission, that he would testify, declare, depose and certify truly, and that any written testimony, declaration, deposition and certificate by him subscribed, would be true, unlawfully, willfully, knowingly, and contrary to such oath, stated and subscribed material matters which he did not believe to be true, namely, the testimony on or about April 1, 2002, and April 18, 2002, the underlined portions of which he believed to be materially false:

Specification One
(Page 96, Line 19 - Page 97, Line 2)

Q: Why did you want to gift shares to [Tippee No. 2]?
A: I had told [Tippee No. 2] that I was going to do that for [Tippee No. 2]. I had told [Tippee No. 2] a couple of weeks before that - [Tippee No. 2] lived off of [Tippee No. 2's] ImClone. [Tippee No. 2] had no other real means of support, and I had told [Tippee No. 2] when we had talked earlier in December about [Tippee No. 2's] financial situation, that I was going to give [Tippee No. 2] more ImClone stock that [Tippee No. 2] could use to live on.

Specification Two
(Page 184, Line 14 - Page 184, Line 24)

Q: The next phone call, 9:22 p.m., who were you calling there?
A: [Tippee No. 1 and another person].
Q: What did you talk about?
A: I didn't. I left a message, I couldn't get a hold of them.
Q: What did you say in your message?
A: "Call me, Sam." I leave [Tippee No. 1] quick messages.
Q: Did you hear back from [Tippee No. 1]?
A: Not that night.

Specification Three
(Page 311, Line 10 - Page 313, Line 8)

Q: Dr. Waksal, I'm handing you what's just been marked as Exhibit 114. Have you ever seen this document before?
A: Yes.
Q: What is it?
A: It's a request to transfer my Merrill account and shares of ImClone to [Tippee No. 2].
. . . .
Q: And the second paragraph says, "It's imperative this transfer take place tomorrow morning, December 27th, first thing." Do you see that?
A: Yes.
Q: Why was it so imperative that the transfer take place?
A: I believe this was just the way this was written, just to make sure that they would do it very quickly. [My accountant] was going away and it was making sure that

it was done immediately. I don't believe that there was any imperative associated with it.

Specification Four
(Page 485, Line 19 - Page 485, Line 25)

Q: Did you ever instruct [Tippee No. 1 or Tippee No. 2] to sell their shares of ImClone?
(a) A: No.
Q: Did you ever suggest to any of them that they sell their shares of ImClone?
(b) A: No.

(Title 18, United States Code, Section 1621).

COUNT TWELVE

(Obstruction of Justice)

The Grand Jury further charges:

51. The allegations of paragraphs 1 through 14, 18 through 19, 21 through 25, 29 through 30, 34 through 43, 47 through 48, and 50 are repeated and realleged as though fully set forth herein.

The Obstructive Conduct

52. After learning of the SEC's investigation, that the SEC had requested the production of documents from ImClone in connection with its investigation, and that ImClone's attorneys had begun to gather documents in response to the SEC's request for production of documents, in or about late January 2002, SAMUEL WAKSAL, the defendant, directed another individual

to destroy certain documents and to delete certain computer files maintained at ImClone's offices in New York, New York. More specifically, WAKSAL directed another person to delete computer files containing phone messages he received, and to destroy certain records pertaining to offshore accounts he maintained in the name of Protec Advisory Group Ltd. at Discount Bank and Trust Company in Geneva, Switzerland, and Amsterdam, the Netherlands.

53. As SAMUEL WAKSAL, the defendant, well knew at the time that he directed the destruction of records relating to his phone messages, such records were material to the SEC's investigation because such records would have revealed the identities of persons to whom SAMUEL WAKSAL may have communicated material non-public information concerning ImClone and described the times and dates of such communications.

54. As SAMUEL WAKSAL, the defendant, well knew at the time that he directed the destruction of documents pertaining to his offshore accounts, such documents were material to the SEC's investigation because such documents may have revealed that WAKSAL unlawfully traded in ImClone securities in offshore accounts and would have revealed the nature and location of assets that the SEC could seek to attach or restrain in a civil

action for disgorgement or penalties for insider trading violations.

55. Pursuant to the direction of SAMUEL WAKSAL, the defendant, in or about late January 2002, the individual deleted certain computer files containing WAKSAL's phone messages. Pursuant to SAMUEL WAKSAL's direction, the individual also deleted computer files and discarded documents evidencing SAMUEL WAKSAL's instructions, among other things (a) on November 6, 2000, to transfer 120,000 shares of ImClone stock to an account in the name of Protec Advisory Group Ltd. at Discount Bank and Trust Company in Amsterdam; (b) on January 10, 2001, to transfer 3,480 shares of ImClone stock to an account at Discount Bank and Trust Company in Geneva; and (c) on September 25, 2001, to wire transfer $2 million to an account in the name of Protec Advisory Group Ltd. at Discount Bank and Trust Company in Amsterdam.

Statutory Allegation

56. In or about late January 2002, in the Southern District of New York and elsewhere, SAMUEL WAKSAL, the defendant, unlawfully, willfully and knowingly, would and did corruptly influence, obstruct and impede, and endeavor to influence, obstruct and impede the due and proper administration of the law under which a pending proceeding was being had before a department and agency of the United States, namely, the SEC,

by directing and causing another person to destroy documents that were material to a pending SEC investigation.

(Title 18, United States Code, Sections 1505 and 2).

COUNT THIRTEEN

(Bank Fraud)

The Grand Jury further charges:

57. The allegations of paragraphs 1 through 3 are repeated and realleged as though fully set forth herein.

Introduction

58. At all relevant times, NationsBank, N.A. was a bank headquartered in Charlotte, North Carolina. During the relevant time period, NationsBank, N.A. merged with the Bank of America, N.A., and was thereafter known as the Bank of America, N.A. (collectively "Bank of America"). At all relevant times, the deposits of NationsBank and Bank of America were insured by the Federal Deposit Insurance Corporation.

59. From in or about April 1999 through on or about January 18, 2002, SAMUEL WAKSAL, the defendant, defrauded the Bank of America, N.A., by pledging certain securities issued to him by ImClone, purportedly worth millions of dollars, to secure approximately $44 million in loans from Bank of America. In truth and in fact, as WAKSAL well knew, after July 20, 2000,

WAKSAL no longer owned those securities he had pledged to Bank of America. Moreover, WAKSAL fraudulently failed to disclose to Bank of America that he had previously pledged those same securities to another creditor. In furtherance of his scheme to defraud, in November 2000, WAKSAL provided Bank of America with a fabricated document containing a forged signature of ImClone's General Counsel, which document falsely represented that WAKSAL still owned those pledged securities.

The Warrant

60. In or about December 1995, ImClone granted to SAMUEL WAKSAL, the defendant, a Stock Purchase Warrant that gave SAMUEL WAKSAL the right to purchase 350,000 shares of ImClone stock at a price of $5.50 per share, during the period from June 12, 1996 through December 11, 2005 (the "Warrant"). At all relevant times, the Warrant was a valuable asset because it permitted WAKSAL to purchase ImClone stock at a price that was substantially below the market price for ImClone's stock. For example, on or about April 21, 1999, the market price for ImClone stock was $17 per share. As a result, the Warrant, which allowed WAKSAL to purchase 350,000 at $5.50 per share, was then worth approximately $4,025,000.

SAMUEL WAKSAL's Pledge of the Warrant to Secure Multiple Debts

61. In or about April 1999, SAMUEL WAKSAL, the defendant, entered into certain credit arrangements with Bank of America ("the Bank of America Credit Facility"). Under the terms of the Bank of America Credit Facility, as modified from time to time, Bank of America extended loans to WAKSAL. As security for those loans, WAKSAL fraudulently pledged certain assets as collateral, including the Warrant. On or about April 21, 1999, WAKSAL assigned all his right, title, and interest in the Warrant to Bank of America.

62. On or about April 21, 1999, the same date that SAMUEL WAKSAL, the defendant, pledged the Warrant to secure the Bank of America Credit Facility, WAKSAL also fraudulently pledged the Warrant to Refco Capital Markets, Ltd. ("Refco"), to secure a short-term credit line extended by Refco to WAKSAL ("the Refco Credit Line"). WAKSAL's contemporaneous pledge of the Warrant to both Refco and Bank of America violated numercus representations and warranties made by WAKSAL both to Refco and Bank of America in connection with the credit extended to WAKSAL by those lenders.

63. At no time did SAMUEL WAKSAL, the defendant, disclose to Bank of America that he had pledged the Warrant to Refco. The failure to disclose this pledge violated the terms of the Bank of America Credit Facility. Similarly, at no time did WAKSAL disclose to Refco that he had pledged the Warrant to Bank of America in violation of the terms of the Refco Credit Line.

64. From time to time during the period from in or about April 1999 through in or about July 2000, Bank of America extended loans to SAMUEL WAKSAL, the defendant, under the Bank of America Credit Facility. As of in or about July 2000, WAKSAL owed approximately $21.8 million under the Bank of America Credit Facility.

65. From time to time during the period from in or about April 1999 through in or about July 2000, Refco extended loans to SAMUEL WAKSAL, the defendant, under the Refco Credit Line. As of in or about July 2000, WAKSAL owed approximately $5 million under the Refco Credit Line.

SAMUEL WAKSAL's Exercise of the Warrant

66. Notwithstanding his pledges of the Warrant to both Refco and Bank of America, from in or about May 2000 through in or about July 20, 2000, SAMUEL WAKSAL, the defendant, exercised the Warrant and purchased all the ImClone stock to which he was entitled under the Warrant. As WAKSAL well knew, after July 20, 2000, the Warrant was fully exercised and had no remaining value. At no time did WAKSAL disclose to Refco or Bank of America that WAKSAL had exercised the Warrant in violation of his pledge of the Warrant as security for the Bank of America Credit Facility and the Refco Credit Line.

67. In or about August 2000, as a condition of continuing to extend credit under the Bank of America Credit Facility, and as a condition of extending additional credit to SAMUEL WAKSAL, the defendant, and to entities he controlled, representatives of the Bank of America requested that WAKSAL provide documentary evidence that the Warrant remained valid and outstanding. In response to this request, WAKSAL forged the

signature of the General Counsel of ImClone on an "Issuer's Letter" dated November 10, 2000, that WAKSAL caused to be transmitted to Bank of America. The forged "Issuer's Letter" falsely and fraudulently represented, among other things, that WAKSAL continued to own the Warrant, when, in truth and in fact, as WAKSAL well knew, the Warrant had been fully exercised and was, at that time, worthless.

68. The fraudulent representations made by SAMUEL WAKSAL, the defendant, regarding his ownership of the Warrant purportedly pledged as collateral for his indebtedness were material to Bank of America. As of July 1, 2001, SAMUEL WAKSAL and entities he controlled owed over approximately $44 million to Bank of America. This entire indebtedness was secured in large part by the Warrant. As of July 31, 2001, Bank of America valued the Warrant at approximately $29.8 million, which accounted for approximately 41% of the total value of the collateral pledged to secure the indebtedness to Bank of America. As of that date, without its knowledge, Bank of America was under-collateralized in that the amount of the debt of WAKSAL and entities he controlled was greater than the true value of the assets pledged to secure the indebtedness. Bank of America was therefore at a risk of loss that it did not knowingly accept.

69. Notwithstanding the fact that SAMUEL WAKSAL, the defendant, had fully exercised the Warrant and nonetheless pledged it to secure his debt to Bank of America, WAKSAL also continued to pledge the Warrant to Refco as security for his growing debt. On or about October 6, 2000 -- approximately two and one-half months after he fully exercised the Warrant -- WAKSAL signed a Terms and Conditions document extending his $5 million credit line from Refco, still pledging the Warrant to Refco as security. In or about January 2001, WAKSAL further agreed that the assets securing the credit line to Refco, would also secure WAKSAL's margin debt of approximately $8.5 million to Refco Securities, LLC, a broker-dealer in New York, New York.

Statutory Allegation

70. From in or about April 1999 up to and including on or about January 18, 2002, SAMUEL WAKSAL, the defendant, unlawfully, willfully and knowingly executed and attempted to execute a scheme and artifice to defraud a financial institution, and to obtain the moneys, funds, credits, assets, securities, and other property owned by, and under the custody and control of, a financial institution, namely Bank of America, N.A., whose deposits were insured by the Federal Deposit Insurance Corporation, by means of false and fraudulent

pretenses, representations and promises, namely, the scheme described above.

(Title 18, United States Code, Section 1344).

/S/
FOREPERSON

/S/
JAMES B. COMEY
United States Attorney

SUPREME COURT OF THE STATE OF NEW YORK

COUNTY OF NEW YORK

51

IMCLONE SYSTEMS INCORPORATED,

Plaintiff,

v.

SAMUEL D. WAKSAL,

Defendant.

Index No. 02/ 602996

SUMMONS

To The Above-Named Defendant:

You are hereby summoned and required to serve upon plaintiff's attorney an answer to the complaint in this action within twenty (20) days after the service of this summons, exclusive of the day of service, or within thirty days after service is complete if this summons is not personally delivered to you within the State of New York. In case of your failure to answer, judgment will be taken against you by default for the relief demanded in the complaint.

The basis of the venue designated is the residence of defendant Samuel D. Waksal, which is 150 Thompson Street, Apt. 5C, New York, New York 10012.

Dated: New York, New York
August 14, 2002

O'MELVENY & MYERS LLP

By: _____
Andrew J. Geist

153 East 53rd Street
New York, New York 10022
(212) 326-2000

Attorneys for Plaintiff
ImClone Systems Incorporated

SUPREME COURT, CIVIL BRANCH, NEW YORK COUNTY

INDEX PURCHASE COVER SHEET

INDEX #: _____

NATURE OF ACTION OR PROCEEDING (check ONE box only and enter on Index Purchase Form)

MATRIMONIAL

[ ] Contested - CM
[ ] Uncontested - UM

COMMERCIAL

[X] Contract - CONT
[ ] Corporate - CORP
[ ] Insurance - INS
[ ] Other Commercial - OC (Other than Contract)
[ ] UCC (including but not limited to Sales, Negotiable Instruments etc.)

TORTS

[ ] Asbestos - ASB
[ ] Breast Implant - BI
[ ] Dental Malpractic - DM
[ ] Medical/Podiatric Malpractice -MM
[ ] Other Professional Malpractice - OPM
[ ] Motor Vehicle - MV
[ ] Negligence - OTN
[ ] Other Tort - OT (including but not limited to Intentional Tort, Environmental, Toxic, Airline, Seamen, etc.)
[ ] Products Liability - PL

REAL PROPERTY

[ ] Condemnation - COND
[ ] Foreclosure - FOR
[ ] Landlord/Tenant - ORP
[ ] Other Real Property-ORP
[ ] Tax Certiorari - TAX

SPECIAL PROCEEDINGS

[ ] Article 75 (Arbitration) - ART 75
[ ] Article 77 (Trusts) - ART 77
[ ] Article 78 - ART 78
[ ] Incompetency - INC
[ ] Guardianship - GUARD
[ ] Other Mental Hygiene-MHYG
[ ] Other Special Proceeding - OSP

OTHER ACTIONS

[ ] Election - ELEC
[ ] Other - OTH

Check "YES" or "NO" for each of the following questions.

Is this action/proceeding against a

YES	NO		YES	NO	
[ ]	[x]	Municipality:	[ ]	[x]	Public Authority:

(specify _____) (specify _____)

YES	NO	
[x]	[ ]	Does this action/proceeding seek equitable relief?
[ ]	[X]	Does this action/proceeding seek recovery for personal injury?
[ ]	[x]	Does this action/proceeding seek recovery for property damage?

B-383

SUPREME COURT OF THE STATE OF NEW YORK
COUNTY OF NEW YORK

IMCLONE SYSTEMS INCORPORATED,

Plaintiff,

- against -

Index No. 02/602496

SAMUEL D. WAKSAL,

Defendant.

COMPLAINT

ImClone Systems Incorporated ("ImClone" or the "Company"), by its undersigned attorneys, for its complaint in this action, alleges upon knowledge as to its actions and upon information and belief as to the actions of all others:

NATURE OF THE ACTION

1. In this action, ImClone seeks disgorgement of funds wrongfully obtained, damages for breach of contract and for breach of fiduciary duty and cancellation of outstanding options, among other relief, against its former director, president and chief executive officer, Samuel D. Waksal ("Waksal").

2. In January 2002 Waksal knowingly took actions to impede or obstruct ongoing investigations by the United States Securities and Exchange Commission (the "SEC") and the United States' Attorney's Office for the Southern District of New York (the "USAO") (collectively the "government investigations") even while at the same time he was reassuring the Company and its board of directors that it was his intention to ensure complete cooperation with

the government investigations by the Company and all of its officers, directors and employees. The Company first became aware of Waksal's actions to impede the government investigations upon its review of the federal grand jury indictment on August 7, 2002.

3. Through his deliberately false and misleading statements to the Company and its board, Waksal induced the Company, among other things, to enter into a separation agreement under which he was paid $7,000,000 and received other benefits (including the immediate vesting of options on over 800,000 shares of the Company's common stock at an exercise price of $50.01 per share) and to advance the fees and expenses incurred by attorneys he had retained in connection with the government investigations and related matters. By this action, the Company seeks disgorgement by Waksal of all compensation paid to him following his breaches of fiduciary duty, of all amounts paid to him under the separation agreement, and of all amounts advanced on his behalf for attorneys fees and expenses pursuant to the Company's certificate of incorporation and by-laws, and seeks cancellation of all other benefits arising under the separation agreement, including cancellation of options and insurance. The Company also seeks recovery of amounts paid in 2002 under Waksal's pre-existing employment agreement (the "Employment Agreement").

PARTIES

4. ImClone is a Delaware corporation with its principal place of business in New York, New York that is engaged in the development and manufacture of biologic medicines. ImClone's common stock is listed on the NASDAQ national market system under the symbol "IMCL."

5. Samuel D. Waksal was one of the founders of ImClone and, until his resignation on May 22, 2002, was a member of the Company's board of directors and was its president and chief executive officer.

VENUE AND JURISDICTION

6. Venue is proper in New York County pursuant to CPLR § 503 because Waksal's principal residence is located in New York, New York.

7. The Court has personal jurisdiction over defendant Waksal because he resides in New York County.

BACKGROUND

8. On December 28, 2001, ImClone issued a press release announcing that it had received a "refusal to file" letter from the Food and Drug Administration with respect to the Company's application for approval of its product Erbitux™ for use by irinotecan-refractory patients suffering from colorectal cancer. In the weeks following this announcement, the price of the Company's common stock declined. A number of purported class actions were brought allegedly on behalf of the Company's stockholders, and a number of purported stockholder derivative actions also were filed.

9. In addition to these civil actions, on or around January 8, 2002, the Northeast Regional Office of the SEC issued to ImClone a request for production of documents and information. In addition to certain other information, the SEC's letter requested production of correspondence with any broker, dealer or financial institution regarding trading in ImClone securities by any ImClone insider. On January 24 and 25, 2002, the office of the U.S. Attorney for the Southern District of New York transmitted to the Company's counsel subpoenas issued by a federal grand jury seeking production of certain documents relating to the same issues. On

January 28, 2002, the SEC issued a formal order of investigation with regard to events surrounding the Company's December 28, 2001 press release and thereafter began to issue subpoenas to ImClone, Waksal and others for the production of information.

10. Upon the receipt of the initial civil complaints and the SEC's request for production of documents and information, instructions were given by the Company to Waksal and others at ImClone to preserve all documents and electronic information that were, or could be perceived to be, relevant to the matters in question. These instructions were repeated when formal subpoenas were received by the Company from the SEC and the USAO.

11. Shortly after the Company received the SEC's first request for production of documents and information on or around January 8, 2002, Waksal assured the Company and its board of directors that it was his intention to cooperate fully with, and to cause the Company and all of its officers and employees to cooperate fully with, the government investigations. Waksal repeated this assurance after the Company received the formal subpoenas from the SEC and the USAO.

12. Directly contrary to these assurances, in or about late January 2002, Waksal directed the destruction of certain documents and computer files maintained at ImClone's offices in New York, New York. These documents and files related to certain of Waksal's telephone communications and personal financial transactions.

13. As a result of that direction, documents and computer files were destroyed. At the time he directed the destruction of records, Waksal knew that such records were, or could be perceived to be, material to the ongoing government investigations.

COUNT I
(Breach of Fiduciary Duty)

14. ImClone repeats and realleges the allegations of paragraphs 1 through 13 as if fully restated herein.

15. At all times when Waksal was the President and Chief Executive Officer of the Company, as well as a member of the Company's Board of Directors, he owed fiduciary duties of loyalty, due care, good faith and full disclosure to the Company.

16. By engaging in the conduct alleged above, Waksal breached those duties, and each such breach was material.

17. Accordingly, the Company is entitled to disgorgement of all compensation paid to Waksal after those breaches occurred.

COUNT II
(Disgorgement of Advancement)

18. ImClone repeats and realleges the allegations of paragraphs 1 through 17 as if fully restated herein.

19. In accordance with the provisions of the Delaware General Corporation Law, ImClone's certificate of incorporation and by-laws provide for indemnification of the Company's directors, officers and employees and for the advancement of attorneys' fees and other defense expenses upon the Company's receipt of an undertaking from such a director, officer or employee pledging to repay amounts so advanced by the Company if indemnification ultimately is not permitted.

20. Thus, section 6.4 of the Company's restated by-laws provides, in pertinent part, that:

> The Corporation shall indemnify to the full extent permitted by law any person made or threatened to be made a party to any action, suit or proceeding, whether civil, criminal, administrative or investigative, by reason of the fact that such person . . . is or was a director, officer or employee of the Corporation . . . . Expenses, including attorneys' fees, incurred by any such person in defending any such action, suit or proceeding shall be paid or reimbursed by the Corporation promptly upon receipt by it of an undertaking of such person to repay such expenses if it shall ultimately be determined that such person is not entitled to be indemnified by the Corporation.

(Emphasis added).

21. Similarly, Article Ninth of the Company's certificate of incorporation, as amended, provides that:

> . . . if the Delaware General Corporation Law requires, the payment of such expenses incurred by a director or officer in his or her capacity as a director or officer . . . in advance of the final disposition of a proceeding, shall be made only upon delivery to the Corporation of an undertaking by or on behalf of such director or officer, to repay all amounts so advanced if it shall ultimately be determined that such director or officer is not entitled to be indemnified under this Article NINTH or otherwise.

(Emphasis added).

22. Section 145(e) of the Delaware General Corporation Law makes clear that the undertaking provided for in these provisions of the Company's certificate of incorporation and by-laws is a prerequisite to advancement of expenses by the Company.

23. On February 27, 2002, Waksal executed an "Affirmation and Undertaking" as a condition to obtaining advancement by the Company of the legal fees and defense expenses incurred on his behalf in connection with the ongoing SEC investigation, the

civil actions, the USAO investigation and an investigation by the Subcommittee on Oversight and Investigations of the U.S. House of Representatives Committee on Energy and Commerce.

24. In the Affirmation and Undertaking, Waksal stated the following:

> I hereby affirm my good faith belief that, with regard to the facts and transactions at issue in the Litigation Matters, I have conducted myself in good faith and in a manner I reasonably believed to be in or not opposed to the best interests of the Company.

The term "Litigation Matters" was defined in the Affirmation and Undertaking and expressly included the SEC investigation, the investigation by the U.S. Attorney's Office and the Congressional investigation in addition to the pending civil actions.

25. As Waksal knew, the foregoing affirmation was a necessary prerequisite to obtaining advancement of his legal fees and other defense expenses in connection with the "Litigation Matters," and the Company expressly relied on this affirmation in advancing such fees and expenses on his behalf.

26. However, Waksal knew at the time he gave this affirmation that he had earlier instructed individuals to destroy documents that were, or could be perceived to be, material to the pending government investigations. Waksal knew at the time he gave this affirmation that the Company had determined to cooperate with the ongoing government investigations and that the destruction of such materials was not "in or not opposed to the best interests of the Company," as he had affirmed.

27. ImClone materially and detrimentally relied on Waksal's false affirmation in advancing legal fees and expenses on his behalf.

28. ImClone is entitled to disgorgement from Waksal of all such amounts advanced on his behalf, in an amount to be proven.

COUNT III
(Fraudulent Inducement; Rescission)

29. ImClone repeats and realleges the allegations of paragraphs 1 through 28 as if fully restated herein.

30. On May 22, 2002, Waksal resigned from his positions as director, president and chief executive officer of the Company. In connection with his resignation, Waksal and the Company entered into a Separation Agreement dated as of May 22, 2002 (the "Separation Agreement").

31. Under the Separation Agreement, Waksal was paid $7,000,000 in separation compensation and received a number of other benefits, including medical and life insurance. The Company also agreed that, notwithstanding the provisions of any stock option plan or agreement to the contrary, any outstanding but unvested stock options would immediately vest and become exercisable. At the time of his resignation, Waksal held approximately 833,332 unvested options having an exercise price of $50.01 per share. As a result of this provision, Waksal's 833,332 unvested options vested.

32. As Waksal knew, the Company would not have entered into the Separation Agreement if it knew that he had earlier ordered the destruction of documents and electronic material that was, or could be perceived to be, material to the ongoing government investigations.

33. Rather than disclosing his direction to destroy documents in negotiating the terms of his separation from the Company, Waksal expressly assured the board of directors that he had done nothing wrong and thereby fraudulently induced the Company to enter into the Separation Agreement.

34. Because it was fraudulently induced, and because the fraud permeated the entire agreement, the Separation Agreement never came into existence. Consequently, the Company is entitled to disgorgement of all amounts paid to Waksal pursuant to the provisions of the Separation Agreement, to cancellation of the stock options that vested pursuant to the Separation Agreement and to cancellation of and repayment by Waksal of all other benefits provided to him under the terms of the Separation Agreement.

35. Alternatively, for the reasons set forth above, the Separation Agreement should be rescinded and the Company should be granted all of the relief specified in the preceding paragraph.

COUNT IV
(Breach of Employment Agreement)

36. ImClone repeats and realleges the allegations of paragraphs 1 through 35 as if fully restated herein.

37. Under the Employment Agreement, ImClone was permitted to terminate Waksal's employment for "cause" for "willful misconduct that is materially and demonstrably injurious economically to the Company." The direction to destroy documents and electronic material, as alleged in this complaint, constitutes "willful misconduct" within the meaning of this provision.

38. As a result of such misconduct, Waksal breached his obligations under the Employment Agreement. For the same reasons, the Company was entitled to terminate the Employment Agreement.

39. As a consequence, the Company is entitled to recovery of Waksal's 2001 bonus and all other amounts paid to him under the Employment Agreement after the date of his instructions to destroy documents and electronic material.

* * * * *

WHEREFORE, ImClone respectfully prays for entry of judgment:

A. Ordering disgorgement by defendant Samuel D. Waksal of all compensation paid to him after his breaches of fiduciary duty.

B. Ordering disgorgement by defendant Samuel D. Waksal of amounts advanced by the Company behalf for attorneys' fees and defense expenses;

C. Ordering disgorgement by defendant Samuel D. Waksal of all amounts paid to him by the Company pursuant to the Separation Agreement;

D. Ordering the cancellation of all stock options, stock appreciation rights or other equity interests in the Company held by defendant Samuel D. Waksal that vested upon his resignation from employment with the Company pursuant to the Separation Agreement;

E. Awarding the Company damages for breach of the Employment Agreement by defendant Samuel D. Waksal equal to the amount of his 2001 bonus and any other payments made to him after he directed the destruction of documents as alleged in this Complaint;

F. Awarding the Company prejudgment interest;

G. Awarding the Company its attorneys' fees and expenses in bringing and prosecuting this action; and

H. Granting ImClone such other and further relief as the Court may deem just and proper.

Dated: New York, New York

August 14, 2002

O'MELVENY & MYERS LLP

By: _____
Andrew J. Geist

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- and -

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Index No. 02/602996

SUPREME COURT OF THE STATE OF NEW YORK
COUNTY OF NEW YORK

IMCLONE SYSTEMS INCORPORATED

Plaintiff,

-against-

SAMUEL D. WAKSAL

Defendant.

Summons and Complaint

O'MELVENY & MYERS LLP
CITIGROUP CENTER
153 EAST 53rd STREET
NEW YORK, NEW YORK 10022-4611
(212) 326-2000

ATTORNEYS FOR
Plaintiff ImClone Systems Incorporated

PRIVLEDGED INTERIM DELIBERATIVE DOCUMENT

Martin, Terry 52 CONFIDENTIAL

From:	Jenkins, John K
Sent:	Thursday, August 29, 2002 6:27 PM
To:	Behrman, Rachel E; Bull, Jonca; Goldberger, Mark J; Houn, Florence; Kweder, Sandra L; Murphy, Dianne; Roberts, Rosemary; Temple, Robert; Albrecht, Renata; Birnkrant, Debra B; Chowdhury, Badrul A; Ganley, Charles J; Katz, Russell G; Love, Patricia Y; McCormick, Cynthia G; Orloff, David G; Pazdur, Richard; Raczkowski, Victor F; Shames, Daniel A; Simon, Lee; Soreth, Janice M; Throckmorton, Douglas C; Wilkin, Jonathan K; Colangelo, Kim M; Collier, Bronwyn E; Locicero, Colleen L; Ripper, Leah W; Roeder, David L; Rumble, Terri F
Cc:	Colangelo, Kim M; Kweder, Sandra L; Jenkins, John K; Yetter, Robert; Johnson, Susan S; Axelrad, Jane A; Woodcock, Janet; Galson, Steven
Subject:	Interim OND Communications Policy Regarding Review of INDs and NDAs

Folks

Attached below is a document that was developed by the Agency in response to recent Congressional interest in FDA communications with sponsors regarding marketing applications, and in particular communication with sponsors regarding potential "adverse" regulatory actions. This document was endorsed by management of CDER and CBER and was presented to and endorsed by Dr. Crawford in a briefing a couple of weeks ago. It was agreed that the principles outlined in this document would be incorporated into the draft guidance to industry and reviewers on "Good Review Management Principles" that is called for under PDUFA III. This will allow public comment on these principles before the guidance is finalized.

I strongly support the principles contained in the attached document and pending finalization of the GRMP guidance the attached document will represent OND policy on such communications. Please familiarize yourself with this new interim policy and educate your staff. As an interim directive, this document is for internal use only and should not be shared outside the Agency

ns

draftcommunic
ionpolicy072302

PRIVLEDGED INTERIM DELIBERATIVE DOCUMENT

DRAFT July 23, 2002
FOR INTERNAL FDA USE ONLY

CONFIDENTIAL

PROPOSED CBER/CDER POLICY ON COMMUNICATING WITH SPONSORS REGARDING MARKETING APPLICATIONS

CBER and CDER recognize the value and importance of communications between the sponsor and the review division throughout the drug development and review process. Such communications allow FDA to provide valuable guidance and advice to sponsors regarding their drug development program and allow FDA to identify deficiencies during the review of a marketing application that may require the sponsor to submit additional analyses or additional data. CBER and CDER believe that communication of advice, guidance, and notification of deficiencies should occur frequently on an as-needed basis as well as during pivotal points during the drug development and review process (e.g., the end-of-phase 2 meeting, the pre-NDA/BLA meeting, during the filing review). While open communication between CBER and CDER and the sponsor are an important part of the drug development and review process, it is important that there be general guidelines that all CBER and CDER review divisions follow to insure consistency of such communications. This is particularly true for communications to sponsors regarding official regulatory actions (e.g., filing decisions, approval/non-approval decisions) since this information may be of a highly sensitive nature and may have significant impact on the financial markets for publicly held companies. With regard to official regulatory actions, the following general principles should govern CBER and CDER communications with sponsors:

1. CBER or CDER officials should not request or suggest to a sponsor that the sponsor withdraw a pending marketing application except in the most unusual circumstances (e.g., the marketing application was submitted to the wrong Center). If CBER or CDER review divisions identify potential serious defects in a marketing application before it is submitted for review (e.g., at the pre-NDA meeting), the sponsor should be clearly informed of such deficiencies in a timely manner. The sponsor should be advised that, if uncorrected, the deficiencies could result in a decision to refuse to file the marketing application. If during the filing review of a submitted marketing application CBER or CDER identify serious deficiencies that may warrant a refuse to file action, the sponsor should be informed of these deficiencies in a timely manner. The sponsor should be advised that the deficiencies, if uncorrected, could result in a decision to refuse to file the application and offered a reasonable opportunity to correct the deficiencies, where that is possible, no later than day 45 of the filing review. Communication to the sponsor that failure to correct a deficiency in the application may result in a refuse to file decision should only occur with concurrence from the review division director. To facilitate timely communication of such deficiencies, informal communications methods may be used (e.g., telephone call, facsimile). However, a record of all such communications must be included in the application file for the record.
2. CBER and CDER will process and review all submitted marketing applications in a manner consistent with a goal of issuing an official written regulatory action (e.g.,

refuse to file, approval, approvable, non-approval, complete response) within the timelines specified in the regulations and the PDUFA goals letter. CBER and CDER believe that the integrity and the transparency of the review process are best served by issuance of an official written regulatory action following an appropriate review of the application. The official written regulatory action, signed by the designated signatory authority, provides an official record of the Agency's decision following review of the marketing application. The official written regulatory action also contains important information regarding the Agency's basis for its approval decision in cases where the application is approved, or complete information regarding the Agency's decision to refuse to file or not approve an application and information needed to correct the deficiencies identified in such cases. While a sponsor may voluntarily withdraw a marketing application at any time after it is submitted for review, CBER and CDER believe that it is generally preferable that applications not be withdrawn by the sponsor and that an official written regulatory action be issued documenting the Agency's review of the application. In cases where a sponsor voluntarily withdraws a marketing application in advance of an "adverse" regulatory action (e.g., RTF, non-approval), CBER and CDER will acknowledge the sponsor's withdrawal of the application in writing. The withdrawal acknowledgement letter will generally include the deficiencies identified by the review division at the time the application was withdrawn.

3. A decision regarding the official regulatory action for an application can only be made after the signatory authority for the application has completed his/her review of the available information (e.g., action package) and his/her consultations with appropriate members of the review team and management. Therefore, communications with the sponsor during the review of the application should generally be related to requests for additional information (e.g., information request letters), identification of deficiencies identified during review that might need to be corrected before the application can be approved (e.g., discipline review letters), and comments regarding draft labeling. In communicating deficiencies identified during the review and comments on draft labeling, CBER and CDER review divisions should make clear to the sponsor the preliminary nature of the communications and the fact that a decision regarding the official regulatory action for the application has not yet been made. Once the signatory authority for the application has made his/her decision regarding the official regulatory action for the application, this decision should be communicated in writing to the sponsor in the form of an official written regulatory action (e.g., refuse to file, approval, non-approval, complete response). The review division should confirm by telephone that the sponsor has received the official written regulatory action and a record of this should be included in the application file for the record. This approach provides a clear record of the timing of communication of the official regulatory action to the sponsor and provides the sponsor the full text of the official regulatory action so they can fully understand the terms of an approval or the deficiencies identified and what additional information/data are required to support approval.

PeerView in Brief 53

Monoclonal Antibodies Targeting the EGF Receptor Move Forward in Clinical Development

From the proceedings of the Second International Monoclonal Antibody Symposium
August 29–September 1, 2002 • Banff, Alberta, Canada

The epidermal growth factor receptor (EGFR) is now the target of three monoclonal antibodies in clinical trials. EGFR has become an important target for therapy as activation of this receptor results in cellular proliferation and maturation, promotion of angiogenesis and contributes to the metastatic potential of certain tumors. It has been shown also to promote tumor survival by inhibiting apoptosis. The anti-tumor effects of these monoclonal antibodies observed in experimental studies have been supported by results of clinical trials involving cancers of the colon, head and neck, lung, and pancreas. These results are encouraging considering the limitations of current therapies.

Monoclonal antibody therapy has already assumed an important role in routine management of several malignancies, in particular, hematologic cancers. Newly discovered and more specific receptors on the surface of malignant cells can be targeted to interrupt the transduction process that is crucial to tumor growth. The ability to direct monoclonal antibodies to cell surface receptors has resulted in effective control of functions such as cellular proliferation and vascularization. These are both essential elements of the malignant process.

"There is enormous interest in monoclonal antibodies. We could enter 10 patients per day into clinical trials involving monoclonal antibodies," observed Michael Kies, MD, professor of medicine, M. D. Anderson Cancer Center, Houston, Texas. This enthusiasm stems from promising results seen in experimental and clinical trials and from the desire to evaluate new anticancer strategies where traditional therapies continue to fail. In particular, there is a desperate need for more effective therapies for colorectal and lung cancers, Dr. Kies emphasized.

The three monoclonal antibodies targeted at EGFR that have reached clinical trials are Cetuximab (IMC-C225; Erbitux), EMD72000, and ABX-EGF. Cetuximab is the most advanced in clinical testing, having reached phase III trials. All three are being targeted most actively at cancers with high EGFR expression, including those of the colon, head and neck, pancreas, lung, and bladder. Interestingly, EGFR expression has been correlated with a poor prognosis in all of these cancers and it also appears to correlate with an increased resistance to certain chemotherapeutic agents and radiotherapy. Expression of EGFR is associated with decreased overall survival in head and neck, pancreatic, and non-small cell lung cancers (NSCLC) and with an increased risk of metastases in colorectal cancer and NSCLC.

Cetuximab Trials in Colon Cancer: Combination Therapy

Cetuximab has been found to be active as a single agent in colon cancer. Like most monoclonal antibodies, however, its application is expected to be in combination with other therapies. The antibody is given intravenously as a 400 mg/m² initial dose followed by a 250mg/m² weekly maintenance dose, with no hospitalization required. In a phase II trial involving 120 highly treatment-experienced patients with advanced disease, the partial response rate of the combination of cetuximab and irinotecan (Camptosar) was 22.5% on independent radiological review. Stable disease was achieved in 7.5% of patients and lasted for a minimum of 12 weeks. Response rate was independent of EGFR expression levels. However, there was a correlation between the grade of skin rash—the most common side effect of this therapy—and tumor inhibition. Objective response rates climbed from 3.8% in those with no skin rash to 14.0% with grade 1 skin rash, 23.5% with grade 2, and 70.6% with grade 3. A similar stepwise correlation was seen with skin rash and median duration of survival (124, 193, 320, and 395 days, respectively).

"Skin rash may be a marker of EGFR blockade," reported Michael Needle, MD, vice president of Clinical Affairs, ImClone Systems, Inc., Somerville, New Jersey. However, this correlation is not perfect. In a second phase II trial in which cetuximab was used alone in patients with colon cancer refractory to irinotecan, the majority of patients developed a skin rash, but one patient who responded to treatment did not have a skin rash.

Monotherapy

A phase II trial of cetuximab monotherapy in irinotecan-refractory colorectal cancer patients showed a partial response rate of 10.5% and stable disease was achieved in 36.8%, according to Dr. Needle. Grade 3 or 4 toxicities were uncommon among the 57 patients

in this trial. Other than the grade 3 or 4 acne-like rash in 18% of treated patients, toxicity was limited to nausea vomiting in 4% and asthenia in 7%.

Results from these two phase II trials demonstrate that cetuximab is active as BOTH a single agent and in combination with chemotherapy in colorectal disease. Based on the favorable clinical experience, phase III trials are now planned with patients refractory to either irinotecan or oxaliplatin (Eloxatin).

"Studies are needed to define the optimal strategies for the use of this agent in the treatment of colorectal cancer," Dr. Needle reported. "We plan to build on the evidence that the EGFR target leads to anti-tumor effects in colorectal disease."

Cetuximab in Head and Neck Cancer

The EGFR target has also shown promise in other malignancies, particularly those involving the head and neck. In the first phase III trial to be completed, patients were randomized to cisplatin (Platinol) plus cetuximab or cisplatin plus placebo (control group). The overall response rate was 22.6% in those randomized to cetuximab and 9.3% in the control group (p=0.051). Partial responses were achieved in 17% of patients on cetuximab versus 5.6% of those on cisplatin plus placebo. Overall survival curves separated early and remained in favor of the cetuximab-treated group, although the difference fell short of statistical significance.

Rash was the most common side effect and, as in colorectal cancer, was "associated with response", according to Dr. Kies. Summarizing the results of the phase III study, he characterized the toxicity as "manageable", noting that grade 3 or 4 toxicities were similar in the two treatment arms with the exception of rash. Although efficacy did not quite meet conventional definitions of significance, the study was underpowered, noted Dr. Kies. Any improvement in the response seen in the highly treatment-experienced patients entered into this trial can be considered encouraging, he stated.

"There is a lot of promise here," Dr. Kies observed, adding that several ongoing trials will provide greater insight into the relative role of monoclonal antibodies targeted at the EGFR in head and neck cancer.

ABX-EGF and EMD72000 Trial Results

Phase I trials of Cetuximab, ABX-EGF, and EMD72000 have been performed in a variety of cancers, including renal cell, prostate, non-small cell lung, pancreatic, and gastroesophageal cancers. Initial clinical experience with EMD72000 and ABX-EGF also has been favorable, and both products are moving into phase II studies. In 131 patients treated with EMD72000 so far, the most common side effect has been rash. The pharmacokinetics of this monoclonal antibody have been predictable, and there has been preliminary evidence of antitumor activity.

"We are encouraged with the antitumor effects observed when EMD72000 is used as a single agent, but down the road I think all of these agents will be better in combination," reported Raj Malik, MD, senior director of clinical oncology, EMD Pharmaceuticals, Inc., Durham, North Carolina. In the initial dose-ranging phase I study, there were no grade 3 or 4 toxicities, and partial responses were observed in patients receiving the higher doses. Phase II trials of EMD72000 are planned, Dr. Malik added.

The first phase II trial of ABX-EGF, another monoclonal antibody directed at EGFR, has already been completed. In heavily pretreated patients with renal cell carcinoma, there were three partial responses and two minor responses in more than 80 patients who received ABX-EGF doses ranging from 1.0 to 2.5 mg/kg. This included shrinkage of pulmonary metastases in one patient. Approximately 50% of patients had stable disease at week 9 of treatment, and the time to progression is still being evaluated.

"The study suggests that ABX-EGF is well tolerated. There was no evidence of anaphylaxis, allergies, or human antibody formation against ABX-EGF. The study also demonstrates single-agent activity," reported Gisela Schwab, MD, chief medical officer, Abgenix, Inc., Fremont, California. As with cetuximab, "there was a tight relationship between response and skin rash", she said. Phase II trials are currently underway or planned in colorectal cancer, non-small cell lung cancer, and prostate cancer.

Small Molecules Targeting EGFR Tyrosine Kinase

The importance of the EGFR signaling pathway has made researchers even more determined to try to block the function of this receptor by various methods. Small molecules—such as ZD1839 (Iressa) and OSI-774 (Tarceva)—which target and inhibit EGFR tyrosine kinase are also in clinical development. This tyrosine kinase is located on the cytoplasmic domain of the EGFR and is activated upon receptor stimulation, permitting the signal transduction cascade that regulates DNA synthesis, as well as cell growth and survival.

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EDITORIAL

Of What Value Is Uracil/Tegafur Plus Leucovorin to Colorectal Cancer Patients?

IN THIS ISSUE OF the *Journal of Clinical Oncology*, there are two "interesting" reports on the use of uracil/tegafur (UFT) plus oral leucovorin in colorectal cancer (CRC) patients.[1,2] I characterize these as interesting because they simultaneously provide both a historical scientific and a contemporary public policy perspective. But before considering either aspect, what was demonstrated by these trials?

Recognizing the need for more effective and convenient CRC therapy, these two industry-sponsored clinical trials evaluated nearly 1,200 patients and yielded consistent, congruent findings. When UFT plus leucovorin was compared with a traditional intravenous bolus fluorouracil plus leucovorin regimen, there were few, if any, efficacy differences detected (given the limits of the sample size considerations). There was a 15% or less objective response rate for both regimens. Likewise, time to progression (approximately 4 months), median survival (approximately 1 year), and opportunity for secondary chemotherapy (approximately half) were monotonously similar. The authors detected no statistical and certainly no medical differences in efficacy to favor one regimen over the other. These regimens did, however, have distinctly dissimilar safety profiles. For a variety of objective measures of toxicity, the UFT treatment was superior. In terms of hematologic toxicity (severe or febrile neutropenia or documented infection), UFT was less toxic. It also had less stomatitis, nausea, vomiting, and diarrhea, although it did have more bilirubin elevation. In essence, both studies concluded that UFT plus leucovorin offered a more favorable therapeutic ratio.

What conclusions should readers draw from these reports? Certainly, that both regimens are unsatisfactory from an efficacy standpoint (but we have long known that about simple fluoropyrimidine regimens). While either could provide the basis for building additional combination programs, the superior safety margin of the UFT regimen might make it more attractive. In a fragile or toxicity-averse or geographically isolated patient, UFT should be the simplest therapy requiring the least monitoring for the same (low) chance of benefit as a Mayo Clinic–type program.

Given the modest nature of these findings and conclusions, what is the historic interest? These studies were the product of their time (1995 to 1997), a time of fewer demonstrated options for CRC patients. Today, we do not encounter large, randomized comparisons of simple fluoropyrimidine regimens in patients with chemotherapy-naive metastatic CRC. The efficacy of irinotecan and oxaliplatin means that combination therapy has become the de facto standard globally. With the testing of a growing number of new agents targeting epidermal growth factor receptor, angiogenesis, and cyclo-oxygenase 2, among others, it is inevitable that clinical research will become increasingly more complicated.

To me, given the limited therapeutic import, the public policy considerations are more worthy of consideration. UFT remains unavailable in the United States because the Food and Drug Administration (FDA) had reservations about its effectiveness. I do not intend to revisit that decision (or the underlying assumptions, analyses, or data that led to that conclusion) but rather to consider UFT as an example of how we, as a nation, arrive at such decisions. Simply put, what should be the basis for the regulatory review of a product that cures no one with metastatic CRC (and even fails to shrink tumors in most patients) but seems to have similar efficacy to other approved regimens? What value should be given to less toxicity? These are not hypothetical questions. From the two studies in this issue, it is hard to argue that UFT is meaningfully inferior to a standard, bolus fluorouracil/leucovorin regimen in terms of efficacy, although it could be very slightly so. It does, however, definitely seem to be better tolerated.

The FDA has the legal authority to approve a new drug product if it is judged to be "safe and effective," but who, I wonder, has the responsibility for that judgment? I would suggest that in our republic, we all do—physicians, insurers, average citizens, and, most importantly, patients themselves. There are no absolutely clear, self-contained standards for the review of a palliative product like UFT, in contrast to a product that cures patients. The judgment of sufficient similarity (or noninferiority) should be made, for this type of drug, on an integration of a complex set of efficacy, toxicity, cost, convenience, and personal preference considerations. For a product that benefits so few, for so brief a period of time, we might better invest our energy in understanding why certain patients benefit, rather than numerically defining the exact minority of a heterogeneous patient population who evidence that response. This should not be treated like one of Xeno's paradoxes.

The FDA tries to protect and promote the public health—a formidable set of aspirations. As it struggles with difficult decisions, the FDA sometimes utilizes advisory committees with expert and lay public input. But, too many of their decisions seem individually and opaquely crafted, at least to an external viewer. The FDA has not articulated a

clear algorithmic roadmap of how it considers the most imperfect products. There seems to be inconsistency between the approval criteria for drugs with similar clinical characteristics intended for the same patient population—such as oral fluoropyrimidine products like UFT and capecitabine for CRC patients. Well-defined guidance that reflects our societal expectations in order to devise proper clinical development programs would be most welcome. Importantly, developing such guidance would provide a venue for citizens to convey their expectations of what they consider safe and effective. This is not scientific relativism or the erosion of research standards. The fact that UFT is approved for use in nearly every country with a sophisticated medical infrastructure indicates that different value systems and public expectations do obtain. Although others have, I see no utility in criticizing the FDA for this particular decision, but we all should expect a more clear, disciplined, formal format that defines how these decisions are rendered. Patients who are so often poorly served by so many of our current treatments should expect to have as many reasonable options as possible. That expectation seems self-evident. The problem will be in clearly defining what is "reasonable."

Michael Friedman
Pharmacia Corp
Peapack, NJ

REFERENCES

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2. Douillard J-Y, Hoff PM, Skillings JR, et al: Multicenter phase III study of uracil/tegafur and oral leucovorin versus fluorouracil and leucovorin in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 20:3605-3616, 2002

2-12-02

WS Journal

To Outsiders, Insider Choices Don't Add Up

By Joseph T. Hallinan

HEARD ON THE STREET

AT IMCLONE, THE MAGIC NUMBER was three. That is how many executives the drug company required to report their ImClone Systems Inc. stock transactions to the Securities and Exchange Commission as corporate "insiders." Among those not considered to be an insider: ImClone's top lawyer.

How can that be?

At a time of hand-wringing about the adequacy of corporate disclosure, companies enjoy a great deal of leeway in deciding how many executives are insiders for purposes of reporting stock transactions to the SEC under a provision known as Sec. 16. At Caterpillar Inc., for instance, there were 39 employee insiders as of the end of its most recent fiscal year. At Boeing Co., there were 15. At Walt Disney Co., there were just seven. That ties it with DuPont Co. for the fewest management insiders at any company in the Dow 30.

Not being an insider doesn't make it legal to trade on confidential information. But these judgment calls are important because trading by insiders is keenly watched by outsiders. "It's very useful because it signals what the insiders perceive to be the future prospects of the company," says Marc I. Steinberg, a securities-law specialist at Southern Methodist University in Dallas.

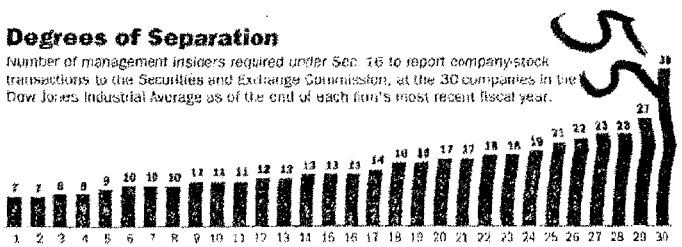
And the fewer insiders required to file reports, the less the information the marketplace has. Critics in the ImClone case, for instance, say they might have suspected insider trading more quickly if they had known that the company's head lawyer and five others had sold millions of dollars in stock after the company had learned its new drug application might be rejected. The company's CEO, Samuel Waksal, has since been charged with tipping off family members to the impending regulatory rejection. A company spokesman has said the firm couldn't comment on stock transactions by its officers.

Asked about its relatively low number of insiders, a Disney spokeswoman says the company is "very, very restrictive." A DuPont spokesman

Please Turn to Page C3, Column 1

Degrees of Separation

Number of management insiders required under Sec. 16 to report company-stock transactions to the Securities and Exchange Commission, at the 30 companies in the Dow Jones Industrial Average as of the end of each firm's most recent fiscal year.



	COMPANY	INSIDERS	COMPANY	INSIDERS	COMPANY	INSIDERS
1	Walt Disney	7	11	Coca-Cola	11	21	3M	17
2	DuPont	7	12	Hewlett-Packard	12	22	Eastman Kodak	18
3	Home Depot	8	13	Intel	12	23	Merck	18
4	International Paper	8	14	American Express	13	24	United Technologies	19
5	Alcoa	9	15	Johnson & Johnson	13	25	Exxon Mobil	21
6	Honeywell	10	16	SBC Communications	13	26	General Electric	22
7	McDonald's	10	17	J.P. Morgan	14	27	IBM	23
8	Wal-Mart	10	18	Boeing	15	28	Microsoft	23
9	AT&T	11	19	Philip Morris	16	29	General Motors	27
10	Citigroup	11	20	Procter & Gamble	17	30	Caterpillar	39

Source: International Strategy & Investment

Continued From Page C1

says its choice of insiders "reflects the corporate management structure of DuPont."

SEC spokesman John Heine says the agency's definition "is specifically designed to ensure that company officials intended to be subject to ... reporting requirements are included regardless of their formal title." The SEC says the proper focus should be whether the person performed "important executive duties" of such character that he or she would be likely "to obtain confidential information about the company's affairs that would aid him if he engaged in personal market transactions."

The rules stipulate no minimum number of insiders. Three titleholders must be designated as "officers," the official term for insiders: the president, the principal financial officer, and the principal accounting officer or controller. Beyond this troika, employees are to be considered insiders if they are vice presidents in charge of a principal business unit such as sales or if they perform a policy-making function.

HEARD ON THE STREET

The discretion comes in deciding what's a "principal" unit and who really sets policy. At many corporations, the answer is precious few.

At the end of its most recent fiscal year, for instance, McDonald's Corp. had 385,000 employees world-wide. But it considered only 10 to be insiders under Sec. 16. International Paper Co. had 100,000 employees world-wide, but said only eight were insiders.

Barbara Smithers, corporate secretary for International Paper, says its number of insiders was chosen by the company's board and reflects the company's management structure. A McDonald's spokeswoman also points to the company's management structure as a determining factor.

At most Dow 30 companies, the company's general counsel is considered an insider—but not at Citigroup Inc. or Hewlett-Packard Co. There, as at ImClone, the lawyers are considered outsiders. A Citigroup spokeswoman says its co-general counsels are expected to be made Sec. 16 insiders by next week. An H-P spokeswoman says its general counsel observes the same internal trading restrictions as the company's CEO and other executive officers.

The general counsel's office isn't the only place where companies' judgments differ. At AT&T Corp., for instance, one of the 11 insiders is its public-relations chief—an understandable choice given that he would know of big announcements before they are publicized. But this isn't the case at Disney. The Disney spokeswoman says its corporate-communications chief, while not an insider for SEC reporting purposes, must nevertheless adhere to the company's insider-trading compliance practices.

Besides those executives designated as management insiders, all company directors as well as those investors who hold more than 10% of a company's shares also must file reports with the SEC detailing their transactions. Still, since the SEC's insider definition is so flexible, says Queenstown University law professor Donald C. Langevoort, a number of top officials with access to confidential information, such as general counsels, may not be required to report stock transactions. "You don't have to be involved in policy-making decisions in order to have your hand in that river of information that runs through the executive suite," he says.

The reporting of insider trades is governed by Sec. 16 of the 1934 Securities Exchange Act. The section was designed to provide the public with information to deter insiders from speculative short-swing trading in their companies' stocks and from engaging in stock trades while in possession of material, nonpublic information.

The SEC's definition of insider was modified after the trading scandals of the late 1980s, one of many reforms at the time. Before the change, the definition emphasized job titles, and sometimes had the effect of requiring filings of everyone with the rank of vice president and up, including people with big titles but no meaningful company role.

The new definition, de-emphasizing job title, took effect in 1991. While last year's meltdown of Enron Corp. in an accounting scandal led to legislation requiring directors and other insiders to report sales and purchases of their own company's stock within two business days, where previously they had as many as 40 days, there appears to be no movement afoot to revise the current definition.

Exactly how much latitude the new standard provides wasn't appreciated until the ImClone imbroglio highlighted that the company had only three management insiders. "That was about as low as I've ever heard," says Peter Romeo, a partner at the Washington law firm of Hogan & Hartson who is generally acknowledged to be one of the nation's leading experts on Sec. 16 issues.

A more typical range of management insiders, he says, is eight to 12. "Anything above or below that is a little unusual." Several months ago, in the wake of the various investigations, ImClone upped its number of management insiders to 11; it now includes the general counsel.

Dow Jones & Co., publisher of The Wall Street Journal, had six management insiders at the end of the year but boosted that number to nine after recent management promotions.

Companies face little prospect of sanction if they fail to count as an insider an executive who meets the SEC's definition. The SEC's Mr. Heine says he knows of no situation "where we took action against a company because some individual failed to file."

To find out which company officials have been designated insiders, investors would need to call a company, as the SEC says it doesn't require companies to list these insiders in any document filed with it. Obtaining the forms showing buying and selling activity is another burden, as the vast majority of such forms are still mailed to the SEC on paper and aren't widely available because the SEC doesn't post them on its Web site. Investors could go through the cumbersome process of ordering paper copies from the SEC, or paying a data firm for access to them.

The insider reports required by the SEC are of interest not only to investors, but also to regulators. That is because stock sales identified in those reports can signal potential insider-trading violations of antifraud provisions known in shorthand as Rule 10b-5.

Slobodin, Alan

From: Gluckow, Paul C [pgluckow@stblaw.com]
Sent: Wednesday, September 18, 2002 2:17 PM
To: Slobodin, Alan
Cc: Koob, Charles E
Subject: Documents

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Alan: Chuck Koob asked me to get back to you on the three questions you asked regarding the documents that were submitted yesterday.

1. HCEC 28338: We have not seen a version of this document that includes the enclosures referred to in the last paragraph. We are working with the company to try to locate such a copy. I will update you on this once I receive additional information.

2. HCEC 28472: The handwriting is as follows: "paid in 12/00 to SDW without complete documentation ~~as to~~ and resulted in $282K note due on DD [demand] or 6/21/01."

3. HCEC 28476: The handwriting at the top is as follows: "Question: Has Audit Committee Charter been adopted by iMCL B of D?"

Please let me know if you have any additional questions concerning the documents. Thank you. -Paul

Paul C. Gluckow
Simpson Thacher & Bartlett
Lexington Avenue
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PR Newswire

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September 25, 2002, Wednesday

SECTION: FINANCIAL NEWS

DISTRIBUTION: TO BUSINESS AND MEDICAL EDITORS

LENGTH: 707 words

HEADLINE: Biotech CEOs Average $513,000 in Salary and Bonus; Waksal's Package Most Lucrative -BioWorld Releases its Executive Compensation Report for 2003

DATELINE: ATLANTA, Sept. 25

BODY:

CEOs and other executives in the biotechnology industry saw increases in their salaries packages in 2001, but total compensation fell due to a decrease in the value of their options and a reduction in perks.

Notably, ImClone Systems Inc.'s former CEO, Samuel Waksal, who pleaded not guilty to insider trading, obstruction of justice and other charges related to alleged actions he took following setbacks with the cancer drug Erbitux at the end of 2001, received the highest total direct compensation amount among the 227 full-year CEOs included in the just-released BioWorld Executive Compensation Report 2003. He made $1 million in salary and bonus for the year and $72 million from the exercise of options on 2.3 million shares, which he may or may not have sold. Twenty-eight of the CEOs had direct compensation packages that exceeded $2 million, while 12 had a salary and bonus of $1 million or more.

The report includes data taken directly from proxy statements of 259 companies on the compensation packages of CEOs, chief financial officers, research and development heads and on two new categories: heads of business and/or corporate development and top legal officers. Data are provided for all company officials in the areas of base salary, bonus, long-term compensation, potential realizable value of options and value of exercisable in-the-money options.

The average salary plus bonus of the 227 chief executives included in the report increased 9.1 percent to $513,000 for the 2001 fiscal year.

At the same time, the average potential realizable value of stock options for CEOs decreased to $1.7 million from $2.2 million; the average value of long-term compensation fell to $1.3 million from $1.9 million; and exercisable in-the-money options fell to $5.2 million from an average of $6.8 million. "Other" compensation, which includes various perks, fell 52 percent, from $119,000 to $57,000.

The average salary plus bonus paid to biotechnology CFOs in 2001 was $278,000, while the average for R&D heads was $299,000, business/corporate development officials $252,000 and top legal officers $314,000.

The BioWorld Executive Compensation Report 2003, which can be purchased at www.ahcpub.com/61321.html, is published by BioWorld Today, the newspaper of record for the biotechnology industry. BioWorld's website is at http://www.BioWorld.com and features current headlines and news stories; stock quotes; analysis of company and industry data; and more. Pulling from all of the BioWorld publications, the site provides subscribers access to more than 12 years' worth of biotechnology business information. Titles include: BioWorld Today, BioWorld International, BioWorld Financial Watch, The BioWorld Biotechnology State of the Industry Report, The BioWorld Genomics Review, The BioWorld Executive Compensation Report, The BioWorld Phase III Report, and BioScan: The Worldwide Biotech Industry Reporting Service.

BioWorld Today is published by Atlanta-based American Health Consultants, a division of The Thomson Corporation. The Thomson Corporation (www.thomson.com), with 2001 revenues of $7.2 billion, is a global leader in providing integrated information solutions to business and professional customers. Thomson provides value-added information and technology to more than 20 million users in the fields of law, tax, accounting, financial services, higher education, reference information, corporate training and assessment, scientific research and healthcare. The Corporation's common shares are listed on the Toronto Stock Exchange (TSX: TOC).

To order the BioWorld Executive Compensation Report 2003, simply go to www.ahcpub.com/61321.html, or call 1-404-262-5476 or 1-800-688-2421.

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LOAD-DATE: September 26, 2002

THE WALL STREET JOURNAL. ONLINE

September 27, 2002 12:47 a.m. EDT

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PAGE ONE

FROM THE ARCHIVES: September 27, 2002

Four Prestigious Labs Ousted Waksal for Questionable Work

By GEETA ANAND
Staff Reporter of THE WALL STREET JOURNAL

In the world of biotechnology, where sterling scientific credentials are critical to winning investor confidence, Samuel Waksal's bona fides seemed impeccable: a string of research positions at such prestigious institutions as Stanford and Tufts universities and the National Cancer Institute. His decade-long academic career lent credibility to **ImClone Systems** Inc., the biotechnology company he founded in 1985, and to the dozen other scientific ventures he says he has helped start since then.

Missing from Dr. Waksal's official resume is that he was pushed out of each of those research institutions for what former supervisors and others say was misleading and, in one case, falsified scientific work. ImClone's board forced him out of the company in May because of directors' increasing anxiety about his truthfulness and legal problems, according to people close to the board.

Once celebrated as a brilliant immunologist on the verge of launching a revolutionary cancer treatment, Dr. Waksal, 55 years old, stands accused by federal prosecutors of insider trading, his career seemingly in ruins. In December, when he learned regulators would soon turn away his company's cancer-drug application, he allegedly tipped off family members who owned ImClone stock and tried to sell his own shares. One of Dr. Waksal's high-profile friends, home-products executive Martha Stewart, is also under investigation for her sale of ImClone stock in December. Dr. Waksal faces additional charges of perjury, obstruction of justice and bank fraud.

Dr. Waksal has pleaded not guilty and denied all of the allegations. His lawyers have portrayed him as "an accomplished scientist and researcher" who is the victim of circumstantial evidence. The lawyers are negotiating with prosecutors over a potential plea deal that would include a prison term of fewer than the seven to 10 years that the government initially threatened and leniency for his family.

After repeated attempts were made to obtain comment from Dr. Waksal for this article, a spokesman said Thursday he was unavailable. ImClone's stock price has fallen to less than $9 a

TANGLED TRAIL

- Merrill Aide to Plead Guilty, Cooperate on Stewart Probe[5] 09/26/02
- ImClone Ordered 2 Shredders in Same Month Probe Started[6] 09/16/02
- House Panel Turns Up the Heat on Waksal in ImClone Probe[7] 08/20/02
- ImClone Alleges Former CEO Impeded Federal Investigations[8] 08/14/02
- Prosecutors Demand Waksal Get a Seven-to-10-Year Prison Term[9] 07/30/02

COMPANIES

Dow Jones, Reuters

ImClone Systems Inc. (IMCL)	
PRICE	7.19
CHANGE	-0.68
U.S. dollars	4:00 p.m.
Bank of America Corp. (BAC)	
PRICE	55.60
CHANGE	-2.40
U.S. dollars	4:00 p.m.

* At Market Close

share from more than $75 in December, just before Dr. Waksal's world began to fall apart. And the trials of ImClone's cancer drug Erbitux -- the object of intense hope by legions of cancer patients -- are now in disarray.

RESUME QUESTIONS

Deposed CEO of ImClone, Samuel Waksal

Past supervisors say Samuel Waksal was pushed out of a series of research positions after questions arose about his work.

- **1968:** Studies as research trainee at National Institutes of Health
- **1969:** Obtains undergraduate degree from Ohio State University
- **1974:** Graduates from Ohio State University College of Medicine with Ph.D. in immunobiology; does research at Stanford University Medical School
- **1975-1977:** Does research at the National Cancer Institute of the National Institutes of Health
- **1977-1982:** Serves as senior scientist at Tufts Cancer Research Center
- **1982-1985:** Directs immunology lab of Mount Sinai School of Medicine
- **1985-2002:** Serves as president and chief executive officer of ImClone

Dr. Waksal says in his resume that he has published more than 50 scientific papers over the years. But by many accounts, his rise in academia and industry stemmed from an unusual ability to talk conceptually about cutting-edge science and an uncanny power of persuasion.

"Every 100 years, someone like him is born," says Robert Schwartz, a hematologist who supervised Dr. Waksal at Tufts University School of Medicine in the late 1970s and now is a deputy editor of the New England Journal of Medicine. "He's a very persuasive person who can convince you of anything," Dr. Schwartz adds. "Within five minutes, you're begging him to work for you."

That Dr. Waksal was able to land a series of prestigious positions, despite his dubious record, illustrates a broader problem: Tainted scientists can move from job to job without bosses taking aggressive action to derail them. The fear is that a researcher tarred by a negative job review will sue for defamation, says William Terry, former head of the immunology branch of the National Cancer Institute at the National Institutes of Health. He hired Dr. Waksal for a temporary research position in 1975 and later decided not to retain him. "Institutionally, we're under the gun to do no more than give [a prospective future employer] the most basic information. It sets up a situation where the bad eggs can move from one place to another with great facility."

Born in Paris to parents who were Holocaust survivors, Dr. Waksal moved with his family in the early 1950s to Dayton, Ohio, where his father went into the scrap-metal business. Young Sam excelled academically, married his high-school sweetheart and went to college and graduate school at Ohio State University.

Even as a graduate student in immunobiology in the early 1970s, he caught the attention of top researchers. "We were all struck by the extremely bright graduate student," says Irv Weissman, a Stanford professor who met Dr. Waksal during a visit to the Ohio State lab where the younger man worked. In 1974, after a brief stint as a post-doctoral fellow at a scientific institute in Israel, Dr. Waksal landed a choice job at Stanford University, with Dr. Weissman's help.

At Stanford, Dr. Waksal worked in the lab of Leonard Herzenberg, a prominent scientist who invented a widely used machine for analyzing and sorting blood cells. Dr. Herzenberg recalls his employee as "an absolute charmer" who at first struck him as having "a great scientific mind. Sam is absolutely brilliant."

But after a series of strange events, Dr. Herzenberg and his scientist wife, Lee, concluded that the young researcher had misled them. Soon after arriving, Dr. Waksal boasted that for research purposes he had obtained a supply of difficult-to-produce antibodies, which are proteins that fight foreign matter in the body. Dr. Waksal said he got the antibodies from the lab of another well-known scientist, Edward Boyse of the Sloan-Kettering Institute, in New York.

Dr. Herzenberg says he asked Dr. Waksal to share the material with another young researcher who had produced promising results in an experiment using other antibodies. Using Dr. Waksal's antibodies, the other researcher couldn't reproduce his earlier results, Dr. Herzenberg recalls. Then, a lab technician reported finding the remainder of the Waksal antibodies spilled in a refrigerator, making it impossible to test them further.

SPECIAL PAGE

- See the Called to Account page[1]
- For more health news, see the Health Industry Edition[2] at wsj.com/health[3].

"I became suspicious," Dr. Herzenberg says. He questioned Dr. Waksal about the origin of the antibodies. "He said they'd been sent to his home at Ohio State and [added], 'I've got the brown wrapper to prove it.' I said, 'Show me the wrapper.' " Dr. Herzenberg recounts. Dr. Waksal couldn't produce the wrapper, Dr. Herzenberg says.

Dr. Herzenberg says he called Dr. Boyse, who told him he had not provided any antibodies to Dr. Waksal. Dr. Boyse and his wife, Judith Bard, say their records show that their lab did ship Dr. Waksal a batch of antibodies, but four years later, in 1978, after he had left Stanford.

Convinced Dr. Waksal had made up the entire story, Dr. Herzenberg says he asked the younger man to leave his lab later in 1974. Some time later, Lee Herzenberg recalls, Dr. Waksal called and apologized to her. "He called to say he really didn't mean anything bad by anything he'd done, and he wanted to be friends. He said the story about the wrapper was not true," Lee Herzenberg says. She adds that Dr. Waksal told her he was seeking psychiatric help and had changed.

Dr. Waksal made arrangements to move to the National Cancer Institute near Washington. Dr. Herzenberg says he warned Dr. Terry of the NCI about the strange experience with the antibodies. But Dr. Herzenberg says he learned that Dr. Waksal denied there had been any problem at Stanford, and Dr. Terry went ahead with the hiring.

Dr. Terry says he doesn't recall such a conversation with Dr. Herzenberg and suggests that the Stanford scientist may have spoken to someone else at the NCI. Dr. Terry says he can't remember whom he talked to about Dr. Waksal before hiring him, but he says he probably went to scientists at Ohio State who knew the applicant from his student days.

'Extremely Bright'

Dr. Terry remembers Dr. Waksal as "extremely bright, articulate and personable, with a breadth of knowledge on immunology literature." But after Dr. Waksal had held a temporary research post at the NCI for about three years, Dr. Terry says he decided against offering the younger man a permanent job, effectively forcing him to leave. The reason was a disturbing pattern in Dr. Waksal's research.

Dr. Waksal was involved in a large number of projects with other scientists, recalls Dr. Terry. "When the critical time came to deliver his part of the collaboration, there would be a catastrophe

of some sort -- a tissue culture would become contaminated or the mice would develop an infection and have to be killed," Dr. Terry says.

In 1977, Dr. Waksal moved to Tufts to work for Dr. Schwartz, the hematologist, whom he had met at a conference. Dr. Terry says he relayed general negative impressions of Dr. Waksal to Dr. Schwartz, even though under the NCI's policy, he was supposed to affirm only that Dr. Waksal had worked there and state the years of his employment. "The fact that I was not prepared to keep him on was known by Bob Schwartz," Dr. Terry says.

Dr. Schwartz says he doesn't remember such a conversation with Dr. Terry. Dr. Schwartz says that in hiring Dr. Waksal, he relied principally on strong recommendations from two senior scientists who had supervised the younger man during his research in Israel.

Dr. Schwartz recalls that Dr. Waksal had an almost hypnotic effect on him and that he was eager to have him work in his lab. But Dr. Schwartz says he grew suspicious of Dr. Waksal in the late 1970s, after bumping into Wallace Rowe, a virologist who had worked at the National Cancer Institute at the time Dr. Waksal was employed there. "He told me, 'Watch out for Waksal,' " Dr. Schwartz recalls.

The warning, he adds, was like "cold water in my face." Suddenly he began to see a pattern to Dr. Waksal's behavior. "He would tell people the results of experiments [he] never carried out," Dr. Schwartz says. In one case, Dr. Schwartz remembers Dr. Waksal saying he had bred a particular type of mouse for use in experiments. After waiting for a long period to see the mice, Dr. Schwartz says, he finally sent a technician to the breeding room to find it. The technician never found them, and Dr. Schwartz says he concluded "that such a mouse never existed."

Dr. Waksal, he adds, "had an extra gift of creating an illusion."

Henry Wortis, a Tufts immunology professor, says he talked often with Dr. Waksal in the early 1980s, and he, too, was bowled over by his "imagination, creativity and far-ranging knowledge." But much like Dr. Schwartz, Dr. Wortis began to have questions about Dr. Waksal's research. He seemed to have "difficulties in getting the experiments he participated in done in a timely fashion," Dr. Wortis says. In one collaboration, Dr. Waksal was supposed to produce some cell lines for experiments, but he never provided them, Dr. Wortis says.

In 1981, Dr. Waksal's brother, Harlan, then a medical resident at Tufts, was arrested and charged with possessing cocaine with intent to distribute. Harlan Waksal, now 49, and chief executive of ImClone, was convicted of cocaine possession the next year in federal court in Miami, Fla., but an appeals court threw out the verdict after finding he had been illegally searched.

Around the time of the arrest, Dr. Schwartz says, the chairman of the department of medicine at Tufts-New England Medical Center, Sheldon Wolff, complained to him that Sam Waksal, who is not a medical doctor, had covered for his brother by seeing patients at the center. Dr. Wolff has since died. Harlan Waksal declined to comment.

"All of these problems put together made me decide [Sam] Waksal had to go," Dr. Schwartz says. He recalls telling Sam Waksal, "I want you out." Sam Waksal has said in the past that he visited one of his brother's patients but did so only to chat with her.

In 1982, Dr. Waksal landed at Mount Sinai School of Medicine in New York. He was hired to run

an immunopathology lab by Jerome Kleinerman, the chairman of the pathology department. Dr. Kleinerman has since died. Dr. Schwartz of Tufts says that he didn't warn anyone at Mount Sinai about Dr. Waksal because no one called to ask his opinion. Later, after problems developed at the New York school, Dr. Schwartz recalls that "the man who hired and fired him [at Mount Sinai] called to complain. I said, 'Sir, you never asked for a recommendation.' "

Friendly and Charming

At Mount Sinai, Alexandra Bona, a scientist who worked for Dr. Waksal as an assistant professor, says he was friendly and charming. They had lunch twice. "He was young, tall, well dressed," she says. He had good taste, and his office was fashionably decorated, which was unusual at the school, she says.

But one day in 1985, the Waksal lab imploded, she recalls. Returning from lunch, Dr. Bona found "everyone crying and Sam was out of his mind." He and a few technicians had been asked to leave immediately, she says. The circumstances of his departure were kept secret from her, she says, . . and she never learned for certain what had happened.

Mount Sinai says it can only confirm that Dr. Waksal worked in the pathology department in the early 1980s. His file is legally sealed under a confidentiality agreement he reached with Mount Sinai. But a person familiar with the situation says Mount Sinai asked Dr. Waksal to leave because of evidence he had falsified data.

Dr. Bona's husband, Constantin Bona, an immunologist and professor at Mount Sinai, says that before the ouster, he had identified a problem with a paper Dr. Waksal had submitted for publication in a scientific journal. Constantin Bona says Sherman Kupfer, then Mount Sinai's senior vice president of research, had asked him and others to review the paper. "I looked at the results. There were discrepancies," Constantin Bona says. "The results in the end were not the same as the lab books."

Dr. Kupfer confirms that Mount Sinai viewed the discrepancies in the Waksal paper as a serious breach. "Is it lying? Not necessarily. But no scientist will accept it as significant proof of a hypothesis," he says. "It's viewed as misconduct and is dealt with severely."

Dr. Waksal has said in the past that he had some disputes with people at Mount Sinai but denied he was forced out.

The year that he left Mount Sinai, 1985, Dr. Waksal founded ImClone to develop new vaccines, among other things. His brother, Harlan, soon joined him as second-in-command at the company. They set up shop in an office building in Manhattan's SoHo district, buying a long-term lease from a bankrupt shoe manufacturer.

The company, which went public in 1991, struggled until Dr. Waksal met John Mendelsohn, then the chairman of medicine at Memorial Sloan-Kettering Cancer Center. Dr. Mendelsohn, who is now president of M.D. Anderson Cancer Center in Houston, had discovered a potential cancer drug and was searching for a company to bring it to market. Where others were skeptical, he says, Dr. Waksal instantly recognized the potential. "Sam said, 'I want that molecule,' " Dr. Mendelsohn, now on ImClone's board, recalls.

The drug, Erbitux, became ImClone's leading prospect. Top researchers in the country began

experimenting with it and reported encouraging results. Many cancer patients began to pin their hopes on Erbitux being approved for general use.

By all external appearances, Dr. Waksal had made it big. He counted among his friends and business partners Ms. Stewart and financier Carl Icahn, both of whom invested in ImClone. He became chairman of the New York Council for the Humanities and hosted monthly soirees in his swank Soho loft, where guests were invited to discuss current issues of intellectual interest. Attendees included actress Lorraine Bracco and Stephen Gould, the scientist and author, who has since died. Mick Jagger once performed at a Waksal party.

While living a lavish lifestyle, Dr. Waksal was borrowing heavily from his companies. In the early 1990s, he borrowed about $300,000 from ImClone, which had just gone public but had no products and little revenue. He paid back the money.

Two years later, when ImClone was almost insolvent, he borrowed $225,000 from another small company he helped start, Merlin Pharmaceutical Corp. He served as chief executive of Merlin. In 1996, after Merlin had merged with another biotech firm, Somatix Therapy Corp., he still owed the combined company about $200,000, according to Somatix filings with the Securities and Exchange Commission. The next year, another firm, **Cell Genesys** Inc., took over Somatix. Dr. Waksal's loan doesn't appear on any Cell Genesys filings with the SEC. Cell Genesys declined to say whether he repaid the loan.

Later in the 1990s, encouraging Erbitux test results attracted keen investor interest. In his crowning business achievement, Dr. Waksal persuaded drug giant **Bristol-Myers Squibb** Co. to invest $2 billion in ImClone in September 2001. In return, Bristol-Myers received some rights to market Erbitux.

While he was negotiating with Bristol-Myers in the summer of 2001, Dr. Waksal borrowed $18 million from ImClone, with which he bought more of the company's stock and increased the worth of his ImClone stake to nearly $300 million. As a result of the unconventional deal with Bristol-Myers, he was able to sell ImClone stock worth $57 million last fall. It couldn't be determined what profit he enjoyed on the sale.

Significant Problems

When the Food and Drug Administration took the unusual step of refusing last December even to review Erbitux, the agency cited significant problems with the design and execution of ImClone's pivotal trial of the drug. A Bristol-Myers scientist told a House subcommittee in June that its review of ImClone's data last year indicated there was missing evidence on 11 of the 27 patients for whom ImClone had reported positive outcomes. Bristol-Myers and ImClone are still working to get Erbitux approved.

In January, securities regulators began reviewing trading in ImClone shares in the days before the FDA decision was announced in late December. Investigators looked into trades by Waksal family members and certain friends, including Ms. Stewart. Brokers declined to process Dr. Waksal's trades, so he wasn't able to sell before the FDA announcement, according to prosecutors. His family members sold stock valued at a total of about $10 million. Ms. Stewart sold stock valued at about $230,000. All concerned have denied they did anything improper.

On March 4, lawyers for ImClone's outside directors told them Dr. Waksal had signed the

corporation counsel's signature on a **Bank of America** Corp. document in connection with a personal loan, according to people close to the board. Later that month, the lawyers told the outside directors that Dr. Waksal had refused to testify before the SEC, contrary to his promise to cooperate fully with all investigations, the people close to the board say. The 10 outside directors -- the Waksal brothers occupied the other two board seats -- decided to ask him to resign, according to the people close to the board.

In the following days, Dr. Waksal persuaded the board to let him keep his job by promising he would now testify before the SEC, according to the people close to the board. But two months later, on May 21, after learning that the SEC staff had recommended filing a civil fraud lawsuit against Dr. Waksal, the ImClone board pushed him out.

The board agreed to give him a $7 million compensation package on his way out the door. But ImClone has since sued Dr. Waksal in state court in New York to get the money back. In the suit, the board accuses him of making "deliberately false and misleading statements to the company," indicating he was cooperating with federal investigators. Instead, the suit says, he was destroying documents and computer records.

On the morning of June 12, Dr. Waksal was awakened by federal agents who, fearing he might flee, blocked the potential escape routes from his apartment. Once inside his loft, the agents arrested him. In August, a federal grand jury indicted Dr. Waksal on the charges of insider-trading, perjury, obstruction of justice and bank fraud.

Write to Geeta Anand at geeta.anand@wsj.com[4]

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Updated September 27, 2002 12:47 a.m. EDT

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U.S. House of Representatives

Committee on Energy and Commerce

Washington, DC 20515–6115

September 30, 2002

Lester M. Crawford, D.V.M., Ph.D.
Deputy Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr Crawford:

The Subcommittee on Oversight and Investigations is continuing to examine FDA drug-approval issues arising from the investigation of ImClone Systems and its drug, Erbitux.

As a follow-up to the Committee's June 27, 2002 letter on drug approval issues and the Committee staff's August 27, 2002 meeting with FDA, the Committee is interested in obtaining more details about the draft FDA guidance on FDA's communications with companies. Therefore, pursuant to Rules X and XI of the U.S. House of Representatives, please provide the following by October 4, 2002:

1. A copy of the draft FDA guidance on communications with companies.

2. All records relating to any interim policy under the auspices of the FDA's Center of Drug Evaluation and Research Office of New Drugs on communications with companies.

Please note that, for the purpose of responding to these requests, the terms "records" and "relating" should be interpreted in accordance with the attachment to this letter.

Thank you for your assistance. If you have any questions, please contact Alan Slobodin of the Majority Committee staff at (202) 225-2927.

refuse to file, approval, approvable, non-approval, complete response) within the timelines specified in the regulations and the PDUFA goals letter. CBER and CDER believe that the integrity and the transparency of the review process are best served by issuance of an official written regulatory action following an appropriate review of the application. The official written regulatory action, signed by the designated signatory authority, provides an official record of the Agency's decision following review of the marketing application. The official written regulatory action also contains important information regarding the Agency's basis for its approval decision in cases where the application is approved, or complete information regarding the Agency's decision to refuse to file or not approve an application and information needed to correct the deficiencies identified in such cases. While a sponsor may voluntarily withdraw a marketing application at any time after it is submitted for review, CBER and CDER believe that it is generally preferable that applications not be withdrawn by the sponsor and that an official written regulatory action be issued documenting the Agency's review of the application. In cases where a sponsor voluntarily withdraws a marketing application in advance of an "adverse" regulatory action (e.g., RTF, non-approval), CBER and CDER will acknowledge the sponsor's withdrawal of the application in writing. The withdrawal acknowledgement letter will generally include the deficiencies identified by the review division at the time the application was withdrawn.

3. A decision regarding the official regulatory action for an application can only be made after the signatory authority for the application has completed his/her review of the available information (e.g., action package) and his/her consultations with appropriate members of the review team and management. Therefore, communications with the sponsor during the review of the application should generally be related to requests for additional information (e.g., information request letters), identification of deficiencies identified during review that might need to be corrected before the application can be approved (e.g., discipline review letters), and comments regarding draft labeling. In communicating deficiencies identified during the review and comments on draft labeling, CBER and CDER review divisions should make clear to the sponsor the preliminary nature of the communications and the fact that a decision regarding the official regulatory action for the application has not yet been made. Once the signatory authority for the application has made his/her decision regarding the official regulatory action for the application, this decision should be communicated in writing to the sponsor in the form of an official written regulatory action (e.g., refuse to file, approval, non-approval, complete response). The review division should confirm by telephone that the sponsor has received the official written regulatory action and a record of this should be included in the application file for the record. This approach provides a clear record of the timing of communication of the official regulatory action to the sponsor and provides the sponsor the full text of the official regulatory action so they can fully understand the terms of an approval or the deficiencies identified and what additional information/data are required to support approval.

ATTACHMENT

1. The term "records" is to be construed in the broadest sense and shall mean any written or graphic material, however produced or reproduced, of any kind or description, consisting of the original and any non-identical copy (whether different from the original because of notes made on or attached to such copy or otherwise) and drafts and both sides thereof, whether printed or recorded electronically or magnetically or stored in any type of data bank, including, but not limited to, the following: correspondence, memoranda, records, summaries of personal conversations or interviews, minutes or records of meetings or conferences, opinions or reports of consultants, projections, statistical statements, drafts, contracts, agreements, purchase orders, invoices, confirmations, telegraphs, telexes, agendas, books, notes, pamphlets, periodicals, reports, studies, evaluations, opinions, logs, diaries, desk calendars, appointment books, tape recordings, video recordings, e-mails, voice mails, computer tapes, or other computer stored matter, magnetic tapes, microfilm, microfiche, punch cards, all other records kept by electronic, photographic, or mechanical means, charts, photographs, notebooks, drawings, plans, inter-office communications, intra-office and intra-departmental communications, transcripts, checks and canceled checks, bank statements, ledgers, books, records or statements of accounts, and papers and things similar to any of the foregoing, however denominated.

2. The terms "relating," "relate," or "regarding" as to any given subject means anything that constitutes, contains, embodies, identifies, deals with, or is in any manner whatsoever pertinent to that subject, including but not limited to records concerning the preparation of other records.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

OCT - 7 2002

The Honorable James C. Greenwood
Chairman
Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

Dear Mr. Chairman:

Thank you for your letter of September 30, 2002, co-signed by W.J. "Billy" Tauzin, Chairman, Committee on Energy and Commerce, requesting documents related to draft Food and Drug Administration (FDA or Agency) documents on Agency communication with companies.

On October 3, 2002, I had a conversation with Mr. Alan Slobodin of your staff concerning the documents requested in your letter. During this conversation, it was agreed that the Agency would provide the following documents that constitute our interim policy on FDA communication with companies:

- E-mail dated 8/29/02 transmitting an interim communications policy to staff at the Center for Drug Evaluation and Research (CDER).
- The attachment to the 8/29/02 e-mail entitled "Proposed CBER/CDER Policy on Communicating with Sponsors Regarding Marketing Applications."

These documents complete our response to your September 30, 2002 letter.

Under established policy, the Agency does not release documents relating to policies that are under development and have not become final. The enclosed documents contain deliberative process information protected from disclosure to the public under the Freedom of Information Act (5 U.S.C. 552). We request that they be treated as privileged information and that the Committee not publish or otherwise make public these documents in whole or in part.

Thank you again for your interest in this matter. If you have further questions, please let us know. A similar letter has been sent to Chairman Tauzin.

Sincerely,

Amit K. Sachdev
Senior Associate Commissioner
for Legislation

Enclosures

cc: The Honorable John D. Dingell
Ranking Member
Committee on Energy and Commerce
House of Representatives

The Honorable Peter Deutsch
Ranking Member
Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
House of Representatives

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September 30, 2002

OUR FILE NUMBER
410.075-002

WRITER'S DIRECT DIAL
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WRITER'S E-MAIL ADDRESS
jbash@omm.com

VIA HAND DELIVERY

The Honorable W.J. "Billy" Tauzin
The Honorable James C. Greenwood
United States House of Representatives
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515-6115

Re: ImClone Systems Incorporated

Dear Chairmen Tauzin and Greenwood:

In response to requests made by the Subcommittee staff, enclosed are documents evidencing the repayment of the $1 million loan extended by ImClone Systems to A.C.T. Group, Inc. on May 31, 2001, maturing on November 30, 2001. As the documents demonstrate, the loan was repaid with a fully executed stock certificate for 625,000 shares of stock in A.C.T. Group, Inc. on April 11, 2002. These documents are Bates labeled HCEC 36886 through HCEC 36889.

In response to questions from the Subcommittee staff, I can confirm that Sonia Ben-Yehuda was not an employee of ImClone Systems. At various times, she did have access to email.

Also in response to questions from the Subcommittee staff, we have been unable to locate any itineraries, travel documents or other correspondence related to a trip by Dr. Samuel Waksal to St. Bart's in January 2002. However, please note that an American Express bill, previously produced to the Subcommittee at HCEC 34777, indicates a charge at a St. Bart's hotel dated January 21, 2002.

For reasons stated previously, we respectfully request that you accord this letter and the enclosed records confidential treatment.

After conducting searches of company records in accordance with our agreement with the Subcommittee staff, we believe that we have now substantially completed production of documents responsive to your August 19, 2002 letter. We will, of course, continue to produce responsive documents to the Subcommittee as they are discovered. Should you or your staff believe that there are any outstanding issues with respect to the August 19, 2002 letter, please contact us at your earliest convenience.

Very truly yours,

Jeremy B. Bash
for O'Melveny & Myers LLP

Attachments

cc: The Honorable John D. Dingell (via hand delivery)
Ranking Member, Committee on Energy and Commerce
The Honorable Peter Deutsch (via hand delivery)
Ranking Member, Subcommittee on Oversight and Investigations
Alan Slobodin, Majority Staff (via hand delivery)
David Nelson, Minority Staff (via hand delivery)
(All without attachments)

10/4/02 WSJ A1
10/4/02 Wall St. J. A1
2002 WL-WSJ 3407935

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The Wall Street Journal

Friday, October 4, 2002

Whither Erbitux? For Dying Patients, Time Is Running Out

The Cancer Drug Caught Up In ImClone Stock Scandal Remains in Tragic Limbo

By Geeta Anand

As Carl Baertlein's doctor delivered his deadly diagnosis -- inoperable pancreatic cancer -- he also offered a sliver of hope to the 30-year-old California engineer.

"If you stay alive for a year-and-a-half, we'll have a drug to really help you," Tal Pomeroy told his patient in January 2000.

Dr. Pomeroy was talking about Erbitux, the drug under development by ImClone Systems Inc., one of a new generation of potential treatments designed to stop cancer cells from growing by interfering with cell chemistry. With his hopes pinned on Erbitux, Mr. Baertlein has been fighting to stay alive as his cancer spread, first to his liver and then to his lungs.

But Erbitux has been swept into the center of an extraordinary storm. In December, the Food and Drug Administration refused to review ImClone's Erbitux application because its clinical trial was flawed. ImClone's founder and chief executive, Samuel Waksal, resigned in May, three weeks before he was arrested on insider trading and other charges, and investigators are now probing stock sales by his friend Martha Stewart on the eve of the FDA's December announcement. All of that has added heartbreak and turmoil to the thousands of desperately sick cancer patients who are hoping the drug will yet save their lives.

Despite the legal mess, Erbitux is a promising cancer fighter. ImClone licensed the drug from John Mendelsohn, who discovered it in the 1970s when he was a researcher at the University of California in San Diego. Dr. Mendelsohn is now president of the respected M.D. Anderson Cancer Center in Houston and a member of ImClone's board. He declined repeated requests for an interview about the drug's prospects.

Erbitux is one of a class of drugs called epidermal-growth-factor-receptor blockers that attack cancer by disrupting the biochemical switches that turn normal cells into malignant ones. The new drugs are more targeted and seem to have fewer and less-severe side effects than chemotherapy and radiation.

Aside from the study the FDA rejected, Erbitux has shown encouraging results in a handful of small clinical trials, and there have been anecdotal reports of dramatic improvements in a few patients over the years. Also encouraging is the thumbs-up that an FDA advisory panel recently gave the agency for a similar drug manufactured by AstraZeneca PLC in London.

Though they still have faith in Erbitux, some patients and their advocates are quickly losing faith in ImClone and its marketing partner, Bristol-Myers Squibb Co., the New York pharmaceutical giant. Initially, patients and others were angry at the FDA for getting in the way of a potentially life-saving drug. Now their anger is increasingly directed at the companies and at Dr. Waksal. The Wall Street Journal reported last week that before he founded ImClone, Dr. Waksal was pushed out of four research institutions for what former supervisors and others say was misleading and, in one case, falsified scientific work. Dr. Waksal declined repeated requests for comment.

"I don't understand frankly how they could have a drug that showed such promise in early tests and botch everything so badly," says Wayne Armentrout, 65, of McLean, Va. Mr. Armentrout, who is fighting metastasized colon cancer and has hoped to take Erbitux, attended the congressional hearing on ImClone this summer and says he came away deeply disturbed. "The whole thing seems to have been an effort to hype the stock and make money on it," he says. "I don't care how much money they made -- now get us a drug." He was disappointed that Dr. Waksal refused to testify. "I wanted to hear why they botched the clinical trial," says Mr. Armentrout, who says he is surprisingly strong even though he is taking two chemotherapy drugs and his cancer has spread to his liver.

ImClone declined to comment yesterday, but Harlan Waksal, the company's current CEO and Samuel Waksal's brother, has apologized in the past

for the flawed trial and promised to get the drug to market as soon as possible. Samuel Waksal's spokesman has said Dr. Waksal wanted to testify at the congressional hearing but was advised by his lawyers to invoke his Fifth Amendment right not to incriminate himself.

Adding to ImClone's travails, the House Energy and Commerce investigations subcommittee has scheduled another hearing on ImClone for next Thursday.

For the past year, patient-advocacy groups, including the Marti Nelson Cancer Research Foundation, in Vacaville, Calif., have been talking with ImClone and Bristol-Myers Squibb about the framework for a very limited compassionate-use program to allow patients such as Mr. Baertlein, for whom other treatments have failed, to take Erbitux.

The groups complain that the companies have failed to deliver on promises they made on at least four occasions over the past year that they would make the drug available at a particular time through such a program. Under compassionate use, the FDA allows patients with no other treatment option to try experimental drugs before the agency approves them for marketing if companies agree to make them available. AstraZeneca, for example, has allowed 18,000 patients to use its drug Iressa while regulators review the drug.

With ImClone and Bristol-Myers, "there's been delay after delay," says Frank Burroughs, who last year founded the Abigail Alliance for Greater Access to Developmental Drugs in a suburb of Washington. He set up the group after his 21-year-old daughter died of squamous-cell carcinoma while trying in vain to gain access to Erbitux or Iressa, which has been made available only to lung- cancer patients.

ImClone and Bristol-Myers, in a written response to the complaints of foot- dragging, say they "remain committed to moving Erbitux through the regulatory process and bringing this important drug to patients with cancer as soon as possible." They say they aim to get the drug to patients on a compassionate-use basis before year's end.

Trying to regain the faith of investors and patients, ImClone has attempted to distance itself from the public scandal surrounding Dr. Waksal and Ms. Stewart. The company sued Dr. Waksal this summer to recoup the $7 million he was paid when he was pushed out in May.

Addison Woods, 51, of Spring, Texas, diagnosed with colorectal cancer in 1997, has undergone several operations as well as taking chemotherapy drugs and radiation -- in hopes of keeping the cancer in check until Erbitux reaches the market. "All along it was, 'Gosh, there's going to be this novel treatment coming out to help me out,' " says the former sales engineer for a small software company. He watched the Internet for news articles on the progress of the drug in small trials, and last year, he and his doctor developed a treatment plan that involved intensive radiation followed by a few months to recoup -- leading up to what they expected would be the approval of Erbitux in the spring.

Then, in late December the FDA took the unusual step of refusing to even review the application. "It was right there and I was going to try it, and it was just jerked away," he says.

Mr. Woods and others are still seething about the hype around Erbitux that made it appear that the drug was within reach. And he resents the mess Dr. Waksal and the companies have landed themselves in -- "problems created by greed," in his view -- that have distracted the companies. Mr. Woods has had surgery for cancer that had spread to his lungs and stomach area. He is now taking a different experimental cancer drug.

Whether Erbitux will ever be approved is an open question. The FDA rejected the 120-patient clinical trial in colorectal cancer that ImClone submitted because it said there were critical flaws in the design and execution of the study. ImClone and Bristol-Myers are hoping to resubmit their Erbitux application based largely on the results of a clinical trial in colorectal cancer that ImClone's German-French partner, Merck KgaA, conducted in Europe. The results of that trial are expected later this year.

To back up that study, the company is also testing Erbitux by itself in about 250 people, in a clinical trial that began earlier this year. ImClone's original application was based on a trial of Erbitux in combination with a chemotherapy drug. The FDA said the trial didn't provide sufficient evidence of how well the drug acted alone.

ImClone and Bristol-Myers have also said they

intend to start several large clinical trials of Erbitux in various cancers this year to determine whether the drug works.

James Abbruzzese, an oncologist at M.D. Anderson Cancer Center who led a small trial of Erbitux several years ago, says he will participate this year in a large study of pancreatic cancer. "I think Erbitux deserves a good, well- conducted clinical trial to sort out its role," he said.

Meanwhile, Mr. Baertlein, the cancer patient, worries that all of this may take too long. The life expectancy of someone with late-stage pancreatic cancer is four-to-six months and he's been fighting the disease for nearly three years. "I'm trying to hold on," he says. "But I'm running out of time."

Journal Link: Read selected excerpts from the new anthology "Floating Off the Page: The Best of The Wall Street Journal's 'Middle Column' " at WSJbooks.com/floating.

---- INDEX REFERENCES ----

COMPANY (TICKER): Bristol-Myers Squibb Co.; Imclone Systems Inc. (BMY IMCL)

NEWS SUBJECT: Regulation/Government Policy; Crime; Crime/Courts; Newspapers' Section Fronts; Health; Health; Front-Page Stories; Page-One Story; Research & Development; Research/ Development; Dow Jones Total Market Index; Wall Street Journal; English language content; Cancer; Corporate/Industrial News; Content Types; Political/General News (C13 CRM GCRIM FRT HLT GHEA PAG NPAG RND C23 WEI WSJ ENGL GCANCR CCAT NCAT GCAT)

MARKET SECTOR: Consumer Non-Cyclical; Technology; Newswire End Code (NCY TEC NND)

INDUSTRY: Biotechnology; Drug Manufacturers; Medical & Biological Technology; Islamic Index; NASDAQ 100 components (BTC DRG MTC XISL XNQ1)

PRODUCT: Pharmaceuticals (DPH)

GOVERNMENT: Food and Drug Administration (FDA); U.S. Government Agencies (FDA USG)

REGION: North America; New York; United States - New York; United States; United States; Northeast U.S.; United States - California; North American Countries; California; Pacific Rim; Western U.S. (NME NY USNY US USA USE USCA NAMZ CA PRM USW)

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The Washington Post

Friday, October 4, 2002

Financial

ImClone Resumes Tests Of Cancer Drug Erbitux

a Washington Post Staff Writer

ImClone Systems Inc., the biotechnology company embroiled in scandal, has resumed testing in the United States of its cancer drug Erbitux, with plans to enroll at least 250 patients in a trial now getting underway at four medical centers.

Sources said, moreover, that the New York company is putting finishing touches on plans for far larger U.S. tests and for an "expanded-access program" for patients who don't qualify for formal tests. ImClone and its large pharmaceutical partner, Bristol-Myers Squibb Co., confirmed these plans in a written statement in response to inquiries, but offered details.

The future of Erbitux has been in doubt ever since the Food and Drug Administration refused to consider early test results last December, citing concerns with the testing methods. Getting new tests underway could make the experimental drug available to thousands of critically ill Americans with colon cancer. The success of the tests also is important to the future of the ImClone-Bristol partnership, to which New York-based Bristol has committed some $2 billion.

Most patients would be screened to determine whether they are suited for formal tests, the sources said. Those who don't qualify, but have exhausted other treatments, would be eligible for a lottery, a common way of distributing a new drug in short supply. At least 50 new patients a month would receive the drug through the lottery, one source said, but that number would escalate as more drug becomes available.

"Bristol-Myers Squibb and ImClone Systems remain committed to moving Erbitux through the regulatory process, and bringing this important drug to patients with cancer as soon as possible," the companies said in their statement. "Over the coming months, the companies expect to enroll patients in Erbitux clinical trials in multiple tumor types."

formal announcement of the expanded tests is expected within three s, sources close to the companies said. It is likely to be welcomed

cancer advocates, who have pressed for better access to the drug since last year and who have grown increasingly agitated in recent weeks at what they perceived as stalling by ImClone and Bristol.

"They have said repeatedly that they will announce an expanded-access program, but the time frame keeps slipping," said Robert Erwin, a California cancer advocate and biotechnology executive who has met repeatedly with the companies. "There's no business or scientific rationale for a decision to hold it back."

The company, however, may have political reasons for delaying. Two sources said the company is going out of its way to work with the FDA and has held off announcing detailed plans for the new tests to give the agency a thorough chance to review them. That review should be finished by mid-month, the sources said.

ImClone has been embroiled in controversy since late last year, when the FDA rejected a prior company test of Erbitux as inadequate.

Relatives of ImClone's then-chief executive, Samuel Waksal, dumped millions of dollars worth of company shares just ahead of the bad news. Waksal has resigned and been indicted for allegedly tipping them off, and multiple investigations are underway into whether he also tipped off style maven Martha Stewart, his close friend, who sold nearly 4,000 shares just ahead of the bad news.

Waksal has denied wrongdoing, but news accounts have suggested he is negotiating a possible plea bargain with federal prosecutors that would spare his father and daughter from indictment.

ImClone is now being run by Waksal's brother, Harlan Waksal, formerly the No. 2 man and generally perceived as the quieter and more fastidious of the Waksal brothers. His own sales of ImClone stock in early December have been questioned in the investigations, but so far no strong evidence of wrongdoing has emerged. The House Energy and Commerce subcommittee on oversight and investigations has scheduled a new ImClone hearing for next Thursday.

ImClone's new testing program comes as other drug makers have reported disappointing results with treatments that work similarly to Erbitux. Tests are already underway in Europe by an ImClone partner, but it's unclear whether those would be sufficient to win approval of the drug.

The 250-patient test that began in August is a trial of whether Erbitux administered by itself can offer any relief for patients with advanced colon cancer for whom other treatments have stopped working. It is about five times larger than a previous test that suggested the drug could help at least some patients in such circumstances. The new test is being staged by cancer doctors in New York, Dallas, Atlanta and Lakeland,

The criteria for patients who want to enroll are stringent, said Charles Henderson, a cancer doctor in Atlanta who is participating. But people with advanced colon cancer have few options and interest is high, he said, despite all the bad publicity about Erbitux.

"It's a shame that Sam Waksal just totally screwed this up," Henderson said. "I think we in the medical community believe this drug is going to be a valuable addition to our cancer armamentarium."

---- INDEX REFERENCES ----

COMPANY (TICKER): Imclone Systems Inc.; Bristol-Myers Squibb Co. (IMCL BMY)

KEY WORDS: BUSINESS NEWS

NEWS SUBJECT: Washington Post; Newspapers' Section Fronts; Business Stories; Corporate/Industrial News; Economic News; English language content; Dow Jones Total Market Index; Cancer; Health; Political/General News; Health; Corporate Actions (WP FRT BZZ CCAT ECAT ENGL WEI GCANCR GHEA GCAT HLT CAC)

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BY FACSIMILE

October 6, 2002

Re: Loans to Samuel D. Waksal

Alan Slobodin, Esq.
Majority Staff
U.S. House of Representatives
The Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515-6115

Dear Alan:

I write in response to your request for a summary of loans made by ImClone Systems Incorporated to Samuel D. Waksal, Ph. D. ("Sam Waksal").[1]

On October 1, 1992, the Company received a promissory note from Sam Waksal for $275,000 bearing 10% interest. This note arose from personal credit card and other charges ("personal charges") Sam Waksal had incurred that ImClone had paid and that needed to be reimbursed to ImClone.

Sam Waksal gave the company a new promissory note dated April 1, 1993 for $367,000 bearing 10% interest, consolidating into a single note the outstanding note of $275,000 and additional personal charges to be reimbursed to the Company. This note was satisfied on January 31, 1994.

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[1] The information set forth herein, summarizing loans since January 1, 1992, was derived from the company's SEC filings (*e.g.*, 10Q's, 10K's, and Proxy Statements), supplemented by records from the Company.

Sam Waksal gave the Company a promissory note dated March 22, 1995 for $156,479.55 bearing 8% interest to consolidate personal charges that accrued during 1993 and 1994. During 1995 and 1996, Sam Waksal repaid $70,000 of the note. In 1997, Sam Waksal gave the Company a new promissory note in the amount of $110,263.61, converting the outstanding balance from the March 1995 note and personal charges incurred in 1995 and 1996 into a single note bearing 5% interest. This note was repaid in full as of December 31, 1997.

In January 1998, the Company accepted a promissory note from Sam Waksal for $130,957.50 bearing 8.5% interest in connection with his exercise of warrants to purchase 87,305 shares of the Company's common stock. This note was repaid in full by December 31, 2000.

The Company accepted a promissory note from Sam Waksal dated December 21, 2000 for $282,200 bearing 10.5% interest in connection with the bonus overpayment that we have discussed with you previously. This note was repaid in full as of November 14, 2001.

In July 2001, the Company accepted a promissory note from Sam Waksal for $18,178,750 in payment for the exercise price associated with the exercise of stock options and warrants. The note bore interest at the prime rate plus 1% and was adjusted quarterly. This note was repaid in full as of November 14, 2001.

We are not currently aware of any outstanding loans, advances, or promissory notes.

Please feel free to contact me if you have any questions or concerns regarding this matter.

Very truly yours,

Charles E. Koob (MCA)

Charles E. Koob

Dow Jones Business News

Boards Need More Women To Ensure Critical Thinking- Panel

Monday October 7, 3:43 pm ET

BRUSSELS -(Dow Jones)- In order to prevent corporate implosions like those seen at Enron Corp. and WorldCom Inc. , corporate boards need more women.

"It's no accident that women raised the tough questions at Enron and WorldCom, " said Marianne Nivert, former President and CEO of Telia AB . " Throughout their career, women have always stood up for their ideas, and have been some sort of odd person ready to attack the old boys system."

Nivert participated Monday at a conference on corporate governance and disclosure in Brussels sponsored by Dow Jones Newswires.

All participants agreed that boards needed more independent members to be effective, that board members should limit their number of appointments, and that they should be better paid for their work. Other participants on her panel, including the men, agreed with the need for more diversity.

"Let's not supplement the old boards system with a new boys and girls network," said Larry Stone, BT Group PLC's company secretary.

There is a lot to clean up. Martin Varsavsky, chairman and found of Spanish telecom company Jazztel PLC admitted that he knew WorldCom's Bernie Ebbers and Imclone Systems Inc.'s Samuel Waksal. "How come I didn't end up in the middle of a scandal like them?," Varsavsky asked himself.

"I was lucky enough to have a board that said, 'No, you are getting out of line here," he answered. For most companies, insuring independence represents the single most important reform required.

here are only two independent directors, you can be pretty sure the board will be non-forming," said Lutgart Van den Berghe, a member ING Groep NV's non-executive board.

I would agree that independence is needed to insure checks and balances," added Peter

Montagnon, head of investment affairs at the Association of British Insurers.

is doubly essential in a small country like Sweden, where all the board members tend to be er CEOs late in their career, and who went to the same schools," said Telia's Nivert.

Some panelists questioned whether a board could be held responsible for all poor decisions. BT's Stone insisted that it was management, not the board's fault, for making his company's disastrous investments such as buying multi- billion-dollar next-generation mobile phone licenses.

"These were fundamental strategic issues, not governance problems," he said.

Others disagreed.

"Strategy by definition should be governance," said Telia's Nivert.

She and others pushed for board members to become more activist. A good board member shouldn't just read the papers prepared by company. "He or she should try to understand the business and visit various parts of the company," said Nivert.

Pay was another crucial issue. Board members at BT earn GBP30,000 a year. Montagnon of the Association of British Insurers said that this was far too little.

Being a director is a big job and should be well remunerated," he said.

With the extra money, the board members should hire staff, Varsavsky added. "They need to have help in taking on this job because they don't have the time to do it themselves," he plained.

ause serving on a board is a difficult job - and because pay traditionally has been too low - st participants lamented how hard it was to find qualified directors.

I'm amazed anyone would accept such as job," Varsavsky said. He himself said he had turned down several offers to serve.

A final recommendation was to limit the number of boards on which a single person joins. But the panelists didn't agree on how many was appropriate.

Five was right for Stone and Montagnon.

Up to eight was appropriate for Van den Berghe and Nivert.

Only three, countered Versavsky.

-By William Echikson, Dow Jones Newswires; +32 2 285 0134; william.echikson@dowjones.com

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ENCLOSURE A

MEMORANDUM

To: All FDA Staff

From: Murray M. Lumpkin, M.D.
Theresa M. Mullin, Ph.D.
Co-chairs
CBER-CDER Product Consolidation Working Group

Date: 28 October 2002

Re: Definition of Scope of Products to be Consolidated

Last month, Dr. Crawford announced that certain products that are presently regulated by CBER would be consolidated into CDER. This original decision announcement included a general framework for determining product consolidation, and the Consolidation Working Group (CWG) was appointed to develop a plan for implementing this decision.

It is important to stress again that implementing this decision is predicated on merging the best practices - both scientific and procedural - of both centers with respect to review of these products. Clearly, the special science that our CBER colleagues bring to these products and the broad clinical expertise of CDER cannot be underestimated. By organizing the drug development and review process around the disease being treated, informed by specific product and technology expertise, the agency decision process for these products can be made even more patient-centered and science-based.

When one looks at products over which CBER, CDER, and all

of our centers have jurisdiction today, one finds a host of cutting-edge, new wave products that are already or will be soon critical to both twenty-first century public health and to our national biodefense. In CBER, as in CDER and all of our centers, science has always been our most reliable, most impartial, and therefore our most effective means of meeting the public trust with which we have been entrusted. As Dr. Crawford has said: "Science is the basis of our understanding of public health risks; it is the arbiter of our standards; it is the solid basis of our regulations; and it is the guide for our enforcement." It is a tradition manifest throughout this Agency; it is a tradition to which we are all committed and which all of us at FDA will uphold in the years to come.

Thus, as was stated in the initial announcement of this product consolidation, it is planned that the unique product expertise that exists for the consolidated products will follow them. It is vital that individuals who are involved with the products that are being consolidated into CDER understand that they are critical to the success of this effort. Their expertise and skills will clearly be needed to help deliver on our shared commitment to patients and practitioners.

This memorandum is intended to inform our colleagues of the CWG's efforts to date and of Agency decisions reached on Phase One of the implementation plan.

PHASE ONE:

The first task of the CWG was to define more precisely the products and product classes that would be consolidated. This was not an easy task. We know that the time that these discussions have taken may have added to the uncertainty about future roles and responsibilities for the oversight of these products. We are especially appreciative of the patience and understanding of CBER and CDER staff.

After discussions within the CWG, several options for defining the final scope of products to be transferred to CDER were presented to Dr. Crawford. After considering the options, Dr Crawford has now made the following decision.

The following product categories that are presently regulated by CBER will be regulated by CDER (except as noted below):

(a) monoclonal antibodies
(b) cytokines, growth factors, enzymes, interferons -- (including recombinant versions)
(c) proteins intended for therapeutic use that are extracted from animals or microorganisms
(d) therapeutic immunotherapies (some specifics yet to be worked out)

The following products, if presently at CBER, will remain in CBER:

(a) monoclonal antibodies, cytokines, growth factors, or other proteins when used solely as an ex vivo constituent in a manufacturing process / when used solely as a reagent in the production of a product that is under the jurisdiction of CBER,
(b) viral-vectored gene insertions (i.e., "gene therapy"),
(c) products composed of human or animal cells or from physical parts of those cells,
(d) blood, blood components and fractions, and recombinant versions of typical blood component or fraction transfusion products,
(e) plasma expanders,
(f) allergen patch tests,
(g) allergenics,
(h) antitoxins, antivenins, and venoms,
(i) in vitro diagnostics,

(j) vaccines
(k) toxoids and toxins intended for immunization

Based on these general product category classes, all presently licensed/approved CBER products and all presently active CBER INDs have been reviewed. A determination has been made as to whether the licensed/approved product or IND would be under the jurisdiction of CBER or CDER. Initial lists of these products and INDs have been shared with the members of the CWG. It is expected that there will be some minor changes as these lists are further reviewed and as experience with this consolidation initiative grows. In addition, there may on occasion be an individual product that, for unique reasons, may be regulated differently from this general scheme.

This determination of the scope of products that will be consolidated into CDER completes Phase One.

PHASE TWO:

Phase Two of this process began recently with the first discussions of various methodologies to be used to help determine the financial resource implications of the consolidation. Phase Two of the process will require severa weeks to complete and will use time report data and analyses generated by CBER and CDER and the OC during the recent negotiating of PDUFA 3. One of the main issues of Phase Two will be not only to assure that appropriate resources transfer with these products, but also to assure that CBER retains adequate resources to perform the critical oversight of products remaining under its jurisdiction.

PHASE THREE:

Phase Three will be the final phase of the consolidation work group planning process. This phase will entail discussions of the logistics of the transfer and consolidation. A major part of Phase Three of the consolidation planning process will be developing procedures and timelines for actual transfer of review responsibilities for specific licensed/approved products and INDs from CBER to CDER.

Following review of the CWG Consolidation Plan by Drs. McClellan and Crawford, agency management will notify the National Treasury Employees Union in accordance with the collective bargaining agreement and resolve any appropriate issues related to the impact of the implementation of the plan.

COMMUNICATION:

As CWG efforts proceed, we will continue to provide updates such as this one, to Agency staff.

While we remain in the product consolidation planning process, all applications (licensed/approved and IND) remain in CBER as they were prior to the initial announcement of the consolidation initiative. Until such time as FDA announces procedures and timelines for product transfer, FDA staff and industry sponsors should keep in mind that current review responsibilities at CBER and CDER have not changed and remain in effect.

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