DISCUSSION DRAFTS CONCERNING PRESCRIPTION DRUG USER FEE ACT REAUTHORIZATION, MEDICAL DEVICE USER FEE AND MODERNIZATION ACT REAUTHORIZATION, DRUG SAFETY, AND CERTAIN PEDIATRIC PHARMACEUTICAL AND DEVICE LEGISLATION

HEARING

BEFORE THE

SUBCOMMITTEE ON HEALTH

OF THE

COMMITTEE ON ENERGY AND COMMERCE
HOUSE OF REPRESENTATIVES

ONE HUNDRED TENTH CONGRESS

FIRST SESSION

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TUESDAY, JUNE 12, 2007

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

The subcommittee met, pursuant to call, at 10:00 a.m., in room 2123 of the Rayburn House Office Building, Hon. Frank Pallone, Jr. (chairman) presiding.

Members present: Representatives Green, Eshoo, DeGette, Capps, Schakowsky, Hooley, Matheson, Dingell, Deal, Buyer, Wilson, Pitts, Rogers, Sullivan, Murphy, Burgess, Blackburn, Myrick, and Hall.

Also present: Representative Markey.

Staff present: Jack Maniko, John Ford, Virgil Miller, Ryan Long, Nandan Kenkeremath, Katherine Martin, Brin Frazier, Robert Clark, Chad Grant, and Melissa Sidman.

OPENING STATEMENT OF HON. FRANK PALLONE, JR., A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW JERSEY

Mr. PALLONE. I call the meeting of the subcommittee to order. Good morning, everyone. Today the subcommittee is meeting to hear testimony about discussion drafts concerning the Prescription Drug User Fee Authorization, Medical Device User Fee and Modernization Act Reauthorization, Drug Safety, and several proposals to encourage more research into the appropriate use of drugs and devices in pediatric populations. I will note, as a matter of process, that each of these issues has had its own hearing in the subcommittee over the course of the past 6 weeks. We have worked very hard to cover a lot of ground and I want to thank all the subcommittee members for their participation in these hearings and I welcome comments and suggestions on these discussion drafts as we continue to move forward.

I will also note that while we did have a hearing regarding follow-up on biologics, I did not include a proposal in last week's

drafts that would address this issue. I want to stress that this issue is of vital importance and its lack of inclusion should not be viewed as a signal to anyone that the door is closed on this very important topic. I am still very interested in developing a consensus on this issue and I hope to do so in the near future.

Let me just say a few words about each of the discussion drafts that we circulated last week, and I think you all know they were on the Web site. The proposal to reauthorize the Prescription Drug User Fee Act or PDUFA, is largely based on the agreement between the FDA and the industry with a few changes. First and foremost, an additional $225 million in user fees is authorized in the discussion draft. These new fees would be dedicated to post-market safety activities and would build upon the $29 million in additional fees already included in the administration's proposal for post-market safety activities. We also include a provision that would require more transparency in the next PDUFA process by allowing a consumer or patient group to participate in the negotiations between the FDA and the pharmaceutical industry.

Now, like the PDUFA proposal, the discussion draft to reauthorize MDUFMA is also largely based on the proposed agreement between the FDA and the medical device industry, with some modifications. Undoubtedly, the most controversial change is to eliminate the changes to the third party inspection program. I realize that the medical device industry has deep concerns about this provision. Over the last week they have come to see us about it. However, I have not been convinced that these changes are necessary in order to improve participation in the program. No one has been able to show me how or why the policies we are changing act as significant barriers to participation.

And finally, I have a philosophical problem with the idea of liberalizing a program that is designed to privatize the core function of a Government regulatory agency. Other key changes to the MDUFMA proposal include a study of the 510(k) process and an authorization of appropriations for post-market activities.

Now, we have also circulated two draft proposals to reauthorize the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act, which are designed to provide necessary research on the appropriate use of prescription drugs in pediatric populations. While these drafts make a number of changes to the program, the two largest changes are eliminating the sunset provision associated with PREA and including an exclusivity adjustment under BPCA. Also included amongst these drafts are proposals supported by Representatives Markey and Rogers to encourage the development of devices to be used in pediatric populations.

And finally, we included a number of proposals that would improve our drug safety system. I realize that the drug safety provisions will be the most contentious. We saw how contested this debate was in the Senate and it is my hope that we can avoid having a repeat performance in this subcommittee. However, it is very clear that there are gaping holes in the current system and the public has lost a great amount of confidence in FDA's ability to protect them from potentially harmful drugs. We must work diligently to strengthen our Nation's drug safety system and restore the public's trust in FDA.

At the heart of our drug safety proposal is the requirement that all new drugs include a risk evaluation and mitigation strategy, which outline the conditions that need to be put in place to ensure that FDA has the tools necessary to protect consumers from unknown risks associated with a new drug. I realize that not everyone is going to agree with the REM strategy or how we are proposing to implement it. The direct-to-consumer advertising provisions included in the REMS have already caused great anxiety among stakeholders and members and I am certainly open to hearing any concerns you have.

Other provisions included in the drug safety drafts are a new clinical trials registry and results database, which are designed to give patients and providers greater access to the information they need to determine the most appropriate and safest course of treatment. There are also new conflict of interest standards that are designed to ensure that FDA's advisory committees remain impartial and provide the best possible advice when it comes to critical issues that impact public health.

These are the major provisions of the draft we circulated last week in which we will hear more about today. Again, I thank all the subcommittee members for their participation in the hearings we had and I am looking forward to getting your feedback today. I would like to also welcome our witnesses here today. We are eager to hear from you and hear your opinions and whatever suggestions you may have.

And now I would recognize my friend, Mr. Deal from Georgia, for 5 minutes for an opening statement.

OPENING STATEMENT OF HON. NATHAN DEAL, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF GEORGIA

Mr. DEAL. Thank you, Mr. Chairman. Many of the pieces of legislation before us today play an important role in ensuring that patients have timely access to approved, safe and effective medications and medical devices. Moreover, some of these drafts encourage the study of medications to meet the special needs of our pediatric population. Historically, these have been bipartisan pieces of legislation and recent action in the Senate on a similar package of proposals demonstrated that the two sides can work together to reach a consensus and preserve patients' access to lifesaving medications.

Unfortunately, as I see the schedule, there is little time for the two sides to work together to move a more largely bipartisan package. I am sure today's hearing will highlight certain aspects of the legislation which could be offered in a way acceptable to both sides. This is especially true on certain reauthorization measures like PDUFA and MDUFMA, which must be passed in order to prevent possible personnel disruptions at the FDA.

It originally was my hope that the chairman would provide the staff enough time to work through these issues prior to our markup. However, with a markup little more than a day from now, I am not sure that is possible. I do look forward to the testimony of our witnesses regarding certain provisions of these drafts. I certainly sympathize with the goal of providing the FDA adequate resources to ensure the safety of the Nation's drug supply. However, making

the agency even more dependent on the industry through an even greater increase in the user fees to achieve this goal may not be the wisest course of action.

I am also concerned that these drafts do not include the suggestions in the original MDUFMA agreement to improve the third party inspection program. Certain changes to the pediatric programs also deserve attention during this hearing. Pediatric device legislation ought to be carefully crafted so that there are not any unnecessary regulatory hurdles which thwart the purpose of the bill. The Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act had been an effective combination to foster the study of medications in children. I have reservations about any attempt to de-link these programs which have successfully promoted the health of the Nation's children.

The drug safety proposals before us deserve important attention during this hearing. I look forward to our witnesses' opinions on these matters in addition to get whatever guidance they can provide on the troubling preemption clause included at the end of some of these drafts. Ultimately, I believe there is room for compromise on these bills. We just need time to allow the negotiation process to work to reach a bipartisan agreement. Holding a subcommittee markup a day from now and a full committee markup a week later, seriously jeopardizes that effort. It takes time for the committee to report good bipartisan legislation, but I am afraid the timeframe we are working in make that virtually impossible. Thank you, Mr. Chairman.

Mr. PALLONE. Thank you, Mr. Deal. Mrs. Capps.

OPENING STATEMENT OF HON. LOIS CAPPS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Mrs. CAPPS. Thank you, Chairman Pallone, and thank you to our witnesses, both panels. I want to commend you, Mr. Chairman, and the committee staff for working so diligently on drafting these proposals and taking into consideration our concerns. As you noted, this has been no easy task. One of the hardest things for me, from the beginning, has been the fact that the administration did not bring patients and consumers to their table for negotiations. I, like many of my colleagues, have always prided myself in protecting consumers. It has been quite a journey to draft a proposal that takes in account consumer protections and concerns. But I am confident that the draft we have before us today is an excellent start and I hope that today we can discuss ways in which to protect both consumers and innovations simultaneously. That remains my goal and I believe it is a possibility.

Some of the concerns I still have and which I know many of my colleagues share include these: reducing conflicts of interest, ensuring the integrity of direct-to-consumer advertising, ensuring proper recourse in the event of patient injury. The issue of conflicts of interest is most glaring because I think there is a misconception about what is and what isn't necessary. It is hard for me to hear that the pool of experts is so small that it is near impossible to have a committee free of financial interest of the company whose product is under review.

Because in reality, I have been told that there is another pool of equally competent experts in academia with no financial ties to industry who have not been solicited and who would be willing to serve on advisory committees. Mr. Chairman, I sincerely hope that as we consider the final language to be marked up on Thursday, we are sure to protect the newly crafted language regarding conflicts of interest and reject any attempts to weaken it.

I would even go so far as to say that we should strengthen it further, that is my goal. And I hope some of our witnesses today, I believe they will, do agree with this. I am eager, also, to hear today from our witnesses regarding the integrity of direct-to-consumer advertising. I think there is more progress to be made in the way of crafting a compromise that protects free speech while also ensuring consumer safety. So thanks again for listening to our concerns and I look forward to hearing from our witnesses today. And I yield back.

Mr. PALLONE. Mrs. Wilson was next. I don't know if she is in the back. If not, we will go to Mr. Ferguson. Mr. Ferguson.

Mr. FERGUSON. I will waive, then.

Mr. PALLONE. Ms. DeGette.

Ms. DEGETTE. Thank you, Mr. Chairman. I have many views on these issues, but I think I will save them for the questioning time and waive my opening statement.

Mr. PALLONE. Mr. Burgess was next, but I don't know if he is back, yet. We will go to Mr. Rogers.

OPENING STATEMENT OF HON. MIKE ROGERS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Mr. ROGERS. Thank you, Mr. Chairman. I hope we can come to some better working relationships by next week and before I do that, I want to thank Mr. Markey for working with us on the pediatric devices portion of the bill. He and his staff have been excellent. But in all of the drafts that were circulated, something that didn't come over in the Senate bill, was this notion of preemption of the States and what concerns me most is all the good work that we have done was taken away in kind of a last minute addition that was not in any of the drafts and was not worked with the minority side, something that I think absolutely renders these bills awful and we have made so much progress.

That book of regulations to get a device or a drug to market, you can comply, according to these new additions in this law, you can comply with every single one of these rules and regulations and we are going to get ready to add new ones in addition, and you can comply with all of it and the last minute addition language that was put into these bills last week would mean that I can sue for any reason in a State court. So I have gone through all the compliance costs, I have used up all my intellectual capital investing in the compliance with this—as a matter of fact, the FDA could tell me certain things aren't eligible to be put on labels and you should not do it because I complied with this and I could still get sued in State court for what the FDA told me not to do.

I hope that we can sit down and talk about it. This makes all of this work, all of the good work of so many people absolutely useless. It absolutely will destroy any hope of innovation in moving the

industry forward so that we get some accountability, we get new innovation, we get new devices and we get new drugs to market. I mean, I feel pretty strongly about this, Mr. Chairman, and I hope that in the spirit of openness and working together in a bipartisan way we can have those kind of discussions before these things kind of get dropped in the bowl like this, because if you leave this language, it puts in jeopardy everything that this committee has done over the last few months and I look forward to hopefully we can work through this, take a look at the language. I am sure it was a mistake that it was dropped in, Mr. Chairman and we can work on it and get this language taken out and we will work through it for the markup coming up. Thank you, Mr. Chairman. I yield back.

Mr. PALLONE. Thank you. Ms. Eshoo.

OPENING STATEMENT OF HON. ANNA G. ESHOO, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Ms. ESHOO. Thank you, Mr. Chairman, for holding this legislative hearing on the nine bills that are before us today. All of them are important for ensuring the safety and the efficacy of pharmaceuticals and medical devices available to the American people. Thank you also for including the legislation that will reauthorize two important programs that have helped to increase the number of drugs and biologics tested labeled for use in children, the Best Pharmaceuticals for Children Act, which I have a great source of pride in, and the Pediatric Research Equity Act.

Last week I introduced H.R. 2589, the Improving Pharmaceuticals for Children Act, to reauthorize both of these successful programs. By making a number of improvements to current law, my bill increases the availability of pediatric information to doctors, parents and researchers. It improves transparency and accountability at FDA and of drug sponsors and it enhances postmarket surveillance of pediatric drugs. It also makes permanent the FDA's authority to require pediatric studies. This adjustment is consistent with FDA's permanent authority to require studies of adult formulations.

I have also included many of the recommendations of the GAO, the American Academy of Pediatrics, the Elizabeth Glaser Pediatric AIDS Foundation, and the FDA, in developing the bills. I would like to ask unanimous consent to insert in the record the letters of support.

Mr. PALLONE. Without objection, so ordered.

Ms. ESHOO. Thank you.

Ms. ESHOO. I am also pleased that the committee print includes many of the provisions in this bill and I look forward to working with it to resolve some of the differences.

In the interest of time, I just want to highlight a couple of points with respect to the other bills before us. The funding for FDA's IT system, I think is woefully inadequate. The committee print allocates $4 million specifically the goal, but I think additional funding should be allocated for IT and I want to work with you to provide these resources.

With respect to third party inspections under MDUFMA, I recognize that FDA is not able to conduct all of the inspections it needs to and that the device and the imaging industries are frustrated by this. I think we need to take another look at the user fee and appropriated funds available under MDUFMA and see if we can come up with a better way of enabling direct FDA oversight of the device and the imaging industries. There is a real tension, a push and a pull between the two, a company being able to do it; consumers saying well, this serves them and the whole issue of post-market surveillance in this, I think we can do better at it, so I want to work with you on that.

Finally, I have serious concerns about the risks to public safety presented by direct-to-consumer advertising. I think that the chairman has done a good job for including provisions in both the PDUFA and the REMS committee print that seek to increase funds at FDA for the voluntary review of DTC ads, but most frankly, I think the voluntary review doesn't really add up to very much. I mean, there just isn't any teeth in it, so we make ourselves feel good by saying we don't like it, but it is not going to do anything about it, so I think that we have to take a harder look at that. So I look forward to this hearing. Thank you for the work that has been put into it. I think we still have some more work to do to ferret out some of the points that have already been made by members and I thank the witnesses in advance for their being here and being instructive to us.

Mr. PALLONE. Thank you. You guys are coming in and out on the other side, so I am getting confused. Mr. Buyer is next, but then I guess we will go back to Mr. Burgess. You waive? OK, Mr. Burgess.

OPENING STATEMENT OF HON. MICHAEL C. BURGESS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS

Mr. BURGESS. Thank you, Mr. Chairman, and I will be brief. I am glad we are taking up these bills and starting to legislate on these important issues. The process, so far, my opinion is somewhat strained. I am concerned that the bills have fallen victim to, in some cases, what might even be described as unnecessary partisanship, barring minority staff involvement from the drafting of even the least controversial of these bills is highly concerning, but whatever concerns we have about the process, there is also concerns about the policies in the draft bills we have seen.

First would be the Federal preemption issue. The bills, as drafted, seem to upset the delicate legal balance set up by the FDA rule and would seem to open up the State courts to a situation that might be labeled litigation for all. Secondly, pediatric exclusivity. I am concerned about the revenue triggers set forth in the draft bill and how the FDA would comply with its requirements. Thirdly, the issue surrounding post-market surveillance. I am interested in working with members of the majority to modify the Risk Evaluation Mitigation Strategy. I believe this committee could adopt a more eloquent approach to this important issue.

Finally, the conflict of interest issue. While I believe we should do all we can to limit conflicts of interest in regulatory agencies, I am concerned that the proposal on conflicts perhaps goes too far

the other direction and would limit important technical institutional expertise that is currently available to the FDA. But Mr. Chairman, there are good provisions in the package, as well, and there is work to be done. I hope we can improve on some of the areas and I hope the witnesses here today will help us begin that process. And I will yield back the balance of my time.

Mr. PALLONE. Thank you. The gentleman from Michigan, the chairman of our full committee, Mr. Dingell.

OPENING STATEMENT OF HON. JOHN D. DINGELL, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Mr. DINGELL. Mr. Chairman, thank you for your recognition. Mr. Chairman, first, commendations to you and congratulations on the outstanding leadership that you are providing on this matter and other matters. The staff draft is an excellent one and I commend you for your vigor and the diligence with which you have moved this forward. Mr. Chairman, I have an excellent statement which I am sure everybody is going to want to read, so I ask unanimous consent to put it in the record at this time.

I do have a few comments to make to my Republican colleagues. The committee is under considerable pressure to move a lot of legislation and as a result, we are not able to proceed in the way that I would ordinarily like to do it. I will tell my Republican colleagues and I want them to hear this because it is a statement made with good will. I intend, first of all, to see to it, on this matter, that every possible procedural fairness and opportunity is given to them. I intend to try to work with them. I know you, Mr. Chairman, intend to do the same thing and we will try and come up with, first of all, substance to which the committee may agree.

Second of all, procedures and processes which will enable our Republican colleagues to not only have fair treatment, but to feel assured that they are having fair treatment and also to see to it that when we have completed the legislation, which we will try to do expeditiously, that we have completed legislation which meets with the high standards that this committee has always had and that we will try to see to it that we do so in a way which is marked by good humor and cooperation amongst the two parties. I will tell my Republican colleagues that I intend, myself, and I know you do, to see to it that this process is not only fair, but results in a good piece of legislation. I thank you, Mr. Chairman.

PREPARED STATEMENT OF HON. JOHN D. DINGELL, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Mr. Chairman, thank you for your leadership on these issues and for the opportunity to begin consideration of the staff discussion drafts released by your subcommittee last week. This hearing is an important step in crafting legislation that will affect millions of Americans, young and old, who need a medical device or take a prescription medication.

Many of these programs will expire at the end of the fiscal year, less than 4 months from now. It is this committee's responsibility to ensure that these programs are reauthorized in a timely manner to avoid any personnel disruptions at the Food and Drug Administration. Hardworking, skilled employees at FDA are looking to us to do our job, so they can continue to do theirs.

As we begin this process of reauthorization, we must work towards strengthening the safety and effectiveness of the Nation's supply of drug and device therapies. We must strike the correct balance between allowing patients timely access to new

therapies, while ensuring that those therapies that enter the marketplace are monitored for safety. We must enhance the post-market surveillance of both devices and pharmaceuticals so that if another Vioxx situation should occur, it is caught quickly.

Another important issue that the discussion drafts focus upon is the need for greater resources at FDA. We have heard about this need from a wide range of stakeholders. I agree. This legislation should provide FDA the necessary user fees to provide timely review of new drug applications, biologic license applications, and premarket approvals for devices. Equally important, we must work to ensure that Congress appropriates the funds authorized for FDA.

This subcommittee has held a number of hearings this year on many of the issues contained in the discussion drafts. Those hearings have been very helpful in preparing us to work on these legislative matters. Again, I thank the chairman for holding this hearing on the discussion drafts, and look forward to the testimony of the witnesses.

Mr. PALLONE. Thank you, Mr. Chairman. Mr. Sullivan of Oklahoma. Are you waiving? The gentlewoman from Oregon, Ms. Hooley.

OPENING STATEMENT OF HON. DARLENE HOOLEY, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF OREGON

Ms. HOOLEY. Thank you, Mr. Chairman. The bills before the subcommittee take critical steps to promote the safe and rapid approval of prescription drugs and medical devices. I am pleased to support the enhanced post-market surveillance provisions throughout the bills. I think these bills improve the Food and Drug Administration's capacity to safely approve drugs and devices and then monitor them for continued safety after they reach consumers.

I would now like to turn to a medical device issue that I believe has significant impact with consumers of implanted medical devices. As a patient, I have had bilateral knee replacement. Dozens of my friends and family and thousands of constituents have similarly had surgeries where medical devices were implanted in their bodies. In many cases, those devices provided lifesaving or prolonged benefits. In other instances such as my own, people's quality of life has been greatly improved as a result of implanted medical devices.

However, when a medical device is recalled, too often a patient may never find out there is a problem. Our current system of notifying patients in cases where a device is recalled, is simply deficient. I am particularly concerned about class 1 recalls that the FDA characterizes as having a reasonable chance the product will cause serious health problems or death. Device manufacturers work very hard to ensure their products are safe. Despite the most diligent efforts, products sometimes fail. In cases where a product has a reasonable chance of causing serious health problems or death, I believe that, as a patient, you or I should be informed. That is not too much to ask. If someone could die or suffer serious harm, those patients should be notified.

As we move toward markup, I hope this committee will be able to take sensible and prudent steps to improve patient notification. A first step in that process is to allow the FDA to conclude its work on a unique device identification or UDI. It has been working hard with stakeholder groups for years as it considers how best to implement a UDI system. Such a system would greatly assist in the recall process and also improve supply chain efficiency.

I believe it is critical to encourage the FDA to continue its rulemaking process while not tying their hands as to the manner or system the agency believes will best serve the public interest. With the unique device identification system as a foundation, I believe we can further empower the FDA to engage in a thoughtful rulemaking process to better ensure patients are notified in those instances where the implanted medical devices may malfunction. The key to any such system is to enable those at the FDA with expertise and recalls and notifications to guide the process of strengthening the system. The public health will benefit from patients having more information.

I believe the FDA can develop a prudent and workable system to notify our parents, grandparents, friends and loved ones when their implanted medical devices present a reasonable chance of death or serious health problems. They deserve no less. Thank you, Mr. Chairman.

Mr. PALLONE. Thank you. The gentlewoman from Tennessee, Mrs. Blackburn.

Mrs. BLACKBURN. Thank you, Mr. Chairman. In the interest of time, I will do as many have done and waive my opening statement. I do just want to register my concern with the delay in getting the legislation and the information to us last night, those of us that have healthcare industry and of course, we all have consumers in our districts and I think that the lack of orderly process is something that has been a disappointment to me and I hope that we will see a more timely process as we move forward with consideration and I yield back.

Mr. PALLONE. Thank you. Mr. Matheson.

OPENING STATEMENT OF HON. JIM MATHESON, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF UTAH

Mr. MATHESON. Thank you, Mr. Chairman. I certainly appreciate the opportunity to hear from the witnesses today regarding the discussion drafts. I hope the witnesses will provide some insight regarding the impact the draft legislation will have to improve drug safety, support FDA in its mission and improve access for children to appropriate drugs and devices.

In light of recent adverse examples brought before Congress, I look forward to hearing recommendations from the panel on how best to achieve a balance between innovation and public safety. I am concerned about one item missing from the discussion drafts. Currently, there are no provisions to address antimicrobial resistance, a true issue of drug safety. I appreciate the rich history this committee has regarding concern about this issue.

Mr. Chairman, as you know, I have been working on this issue and look forward to working with you and others of the committee to pass legislation in this area. I plan on introducing to reauthorize and build on a program my colleague, Mr. Stupak, authored with our former colleague, Mr. Burr, section 319(e) of the Public Health Service Act, combating antimicrobial resistance. I hope my colleagues will work with me to include these provisions as we consider FDA legislation. It would be a shame to miss this opportunity to put in place provisions that will help protect us against many

resistant infections that are out there and are placing people in danger.

Antibiotics present unique challenges for drug safety. As we know, they are researched and developed to respond to infectious organisms that continue to mutate and build resistance to the product even after approval. Even if we all demonstrate good judgment and use antibiotics wisely, eventually the bad bugs become resistant. It will take a coordinated effort and a partnership between manufacturers, Federal agencies, providers and patients to truly make a difference in slowing the trend of antimicrobial resistance.

It is my hope that this committee will include provisions to protect antibiotic safety and effectiveness, as well as improve access to new antibiotics. I do think we should make every effort to ensure that people have access to effective new medicines as quickly as possible and with thorough safety guidelines. Mr. Chairman, I will yield back.

Mr. PALLONE. Thank you. The gentlewoman from Illinois, Ms. Schakowsky.

OPENING STATEMENT OF HON. JAN SCHAKOWSKY, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF ILLINOIS

Ms. SCHAKOWSKY. Thank you, Mr. Chairman. I do just have a brief statement. I want to thank you for your leadership, Mr. Chairman, on these critical issues. The legislation we have before us today has the potential to significantly improve the way patients make decisions about the drugs or medical devices they use in a variety of ways. I appreciate the witnesses being here today, I look forward to hearing their insight on the proposals. A lot of work remains here as we work to pass these significant and critical pieces of legislation, but I am confident that the subcommittee has the ability to come to a consensus that is in the best interest of patient safety and scientific integrity.

Clearly, a balance is being sought here, but it is crucial to protecting consumers of drugs and medical devices. We need an efficient process that brings us medicines and devices that are both safe and effective and we need to work to ensure that the agency responsible for overseeing much of this process maintains its integrity and reliability. Without a doubt, within this debate lies the difference between sickness and health and life and death for so many of our constituents. As we move forward, I remain concerned that patients continue to be first and foremost throughout any debate.

I look forward to passing legislation that will truly enhance the way information comes out of the FDA, is made available to the public and is used by all parties involved to improve the health of those who must take prescription drugs or use medical devices. This of course, includes our children and I appreciate the chairman's efforts in making safer pediatric therapies more readily available to this population. I also commend the chairman's work to increase the resources available to the FDA's drug review program and to make significant improvements to both the pre- and post-market safety programs.

Again, I look forward to the work we have ahead of us and anticipate that we will bring positive change and essential improvements to the legislation before us. I yield back.

Mr. PALLONE. Thank you. And I recognize our vice chair, Mr. Green from Texas.

OPENING STATEMENT OF HON. GENE GREEN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS

Mr. GREEN. Thank you, Mr. Chairman, for holding our legislative hearing on this legislation that would reauthorize expiring user fees or approval of both prescription drugs and medical devices at the FDA, as well as several bills that we are going to enact some much needed reforms at FDA. This committee, particularly the Oversight and Investigation Subcommittee, has spent a wealth of time investigating lapses in drug safety at the FDA, specifically with regard to Vioxx, Ketek and antidepressants. These investigations uncovered significant structural and cultural problems at the FDA that these bills should seek to remedy to better ensure the safety of our Nation's drug supply.

I am particularly supportive of the legislation to enact a Risk and Evaluation Mitigation Strategy at the FDA whereby each new drug the FDA approves would be analyzed and a safety profile would be established for that specific drug so that risk and benefits continue to be monitored throughout the life cycle of that drug. This draft includes an important step forward for safety by granting the FDA much needed authority to require post-market studies. The FDA's post-market authority has been sorely lacking. I think a majority of us would agree that this additional authority and a dedicated funding source through the user fee program is a good step forward.

The Risk Evaluation Mitigation Strategy proposal is not without controversy. There is no question that a point of contention remains over the direct-to-market, direct-to-consumer advertising. I, for one, support the language in the discussion drafts that provide the Secretary with the authority to impose a temporary waiting period for the mass advertising of a drug. I understand there may be Constitutional concerns with the language, however I support our chairman in his efforts to have the strongest language possible out of the committee.

There is no question that sales of Vioxx skyrocketed during the direct-to-consumer advertising despite the fact that the drug was indicated for a small subset of individuals who couldn't tolerate other drugs. This temporary advertising waiting period would help us on this post-market side to identify and monitor any adverse events in larger sets of people before a drug is mass marketed for the entire country.

All along we said that additional authority must be met with a cultural change at the FDA and I am glad to see that the subcommittee will take up legislation that addresses the conflicts of interest of the FDA advisory panels. While many of us that prefer that the advisory committee meetings be entirely free of conflicts of interest, I can understand the need to conclude a waiver process to ensure that the panel can gain the appropriate expertise as long as the one waiver and the nature of the panel members financial

interest is made public. I would, however, like to see additional safeguards put into place for FDA scientists to ensure that their scientific opinions are heard and not suppressed for financial or political purposes.

We have heard too many times the FDA scientists consider the drug companies to be clients. Let there be no mistake. The American people are the clients of the FDA and the publicity around supervisors who are telling people not to do it because we need to move these drugs is just wrong and I hope this bill corrects that. The American people are the ones the FDA is supposed to represent, not the people paying those bills. If they don't have the authority to do that, to over see that, they pay it to get the speediest approval possible, but the American people are the ones that the FDA represents and I hope they remember that.

I hope we can work together on these bills and move the process to include strong language to protect the FDA scientists and allow them to do their jobs on behalf of the American people. There are many specific issues in the bill that need to be analyzed and I say these are questions for later and I thank the FDA representatives and the stakeholder groups for appearing today. And also, I would like to thank the chair for your work in moving these bills through the committee, particularly ensuring that each of the issues have benefited from the public hearing process and I will yield back my time.

Mr. PALLONE. Thank you. Mrs. Wilson, did you want to make an opening statement? No? I think that concludes our opening statements, then, so I will now turn to our witness, our first panel. We have with us Mr. Randall Lutter, who is Deputy Commissioner for Policy at the FDA. Welcome you. Thank you for being with us today. I always say that you may, in the discretion of the committee, submit some written responses later or additional material if you can't answer the questions that we pose today, but if you would, I would like you to begin and thank you again for being here.

STATEMENT OF RANDALL LUTTER, DEPUTY COMMISSIONER FOR POLICY, FOOD AND DRUG ADMINISTRATION

Mr. LUTTER. Thank you, Mr. Chairman, and members of the subcommittee. I am Randy Lutter, Deputy Commissioner for Policy at the Food and Drug Administration. I am pleased to be here today to talk about discussion drafts to reauthorize several statutes of vital importance. In my oral remarks, I will highlight only a few areas of concern. Our broader comments and concerns are outlined in written testimony that was also submitted to the committee.

The Prescription Drug User Fee Act has produced significant benefits for public health, including providing the public access to over 1,200 new drugs and biologics since its enactment in 1992. We believe that the administration's proposal places PDUFA on sound financial footing, enhances pre-market review and creates a modern post-market drug safety system that would follow products throughout their full life cycle. We are pleased that the discussion draft is generally consistent with the administration's proposal. One significant concern to us is the lack of clarity about funding new drug safety activities. In our view, the amount that could be

raised through user fees may be inadequate to support the new activities.

Similarly the user fees provided by the Medical Device User Fee and Modernization Act and annual appropriations have allowed us to make significant improvements in the device review program. Since MDUFMA was enacted, FDA has approved more than 150 original pre-market approvals. We believe our proposal would ensure sound financial footing for the device review program and would enhance the process for pre-market review of device applications. We have technical concerns about the discussion draft.

The administration also supports reauthorization of the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act. Together, these statutes have transformed information about safety and efficacy for children of important therapeutics and promoted safety and innovation in pediatric drug development. We are concerned, however, that the discussion drafts contain provisions that could have an unintended and negative impact on these successful programs.

The draft bill's creation of an internal review committee for both BPCA and the PREA functions are of concern. A legislative requirement for what are primarily staff functions is in direct conflict with our expertise, flexibility and efficiency needed to ensure rapid review of pediatric product development. For this reason and for related reductions and incentives to provide appropriate pediatric drug trials, the administration would favor straight reauthorization over the enactment of these provisions. The PREA discussion draft would require FDA to give priority review status for all supplements to new drug and biologics applications submitted as a result of PREA. This would remove the flexibility FDA currently has in determining the appropriateness of the priority designation in relation to other priorities.

With respect to safe and effective pediatric medical devices, FDA is committed to supporting their development and availability. The discussion draft raises several concerns, however. The draft would require FDA to track separately the adverse events associated with for-profit sales versus not for profit sales of pediatric devices. The public health benefit of such a requirement is unclear to us. The draft also would require annual review of for-profit pediatric devices by the Pediatric Advisory Committee. This duplicative review imposes significant burden without a clear public health benefit.

We have a number of concerns with the discussion draft on drug safety. Some changes prescribe a specific agency action without clear public health benefit, such as the requirement to present all new molecular entities to advisory committees for review. We are also concerned about the breadth of the proposed requirements for Risk and Evaluation Mitigation Strategies outlined in the bill. We believe it is unnecessarily burdensome to require REMS and periodic assessments or reassessments for all drugs.

We support the addition of provisions for an active drug safety surveillance system that would be established through a public/private partnership and we want to work with you on this provision to ensure the most effective implementation. We are concerned about new language on preemption in the discussion drafts which state that nothing in the Act may be construed as having any legal

effect on actions for damages under State law, including statutes, regulations and common law. We believe that State law actions that can conflict with agency conclusions and frustrate the agency's implementation of its public health mandate should not be endorsed in Federal laws.

In conclusion, PDUFA III and MDUFMA expire on September 30, 2007. I want to reemphasize the importance of timely reauthorization of these laws in order to avoid disrupting key ongoing and effective programs. FDA is ready to work with you to accomplish this goal. We welcome the opportunity to work with Congress to ensure the benefits of these acts will be enjoyed as Congress considers reauthorization of the BPCA and the PREA programs, as well. Thank you very much, Mr. Chairman.

[The prepared statement of Mr. Lutter follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration

STATEMENT OF

RANDALL LUTTER, PH.D.
DEPUTY COMMISSIONER
FOR POLICY

FOOD AND DRUG ADMINISTRATION
BEFORE THE

SUBCOMMITTEE ON HEALTH

COMMITTEE ON ENERGY AND COMMERCE

UNITED STATES HOUSE OF REPRESENTATIVES

"Legislative Hearing on Discussion Drafts Concerning Prescription Drug User Fee Act Reauthorization, Medical Device User Fee and Modernization Act Reauthorization, Drug Safety, and Certain Pediatric Pharmaceutical and Device Legislation"

June 12, 2007

RELEASE ONLY UPON DELIVERY

Introduction

Mr. Chairman and Members of the Subcommittee, I am Randall W. Lutter, Ph.D., Deputy Commissioner for Policy at the U.S. Food and Drug Administration (FDA or the Agency). I am pleased to be here today to talk about discussion drafts to reauthorize several statutes of vital importance to our mission to protect and promote the public health, as well as enhancements to our current authorities in the areas of pediatric devices and drug safety.

The Administration strongly supports the reauthorization of the prescription drug user fee and medical device user fee programs. These user fee programs expire at the end of September 2007, and their timely reauthorization is critical to the ability of FDA to continue to bring safe and effective drugs, biologics, and devices to market to the benefit of the health of Americans in a timely manner. We also support timely reauthorization of the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA), as these two statutes are essential to gathering much needed information required in the safe and effective use of medicines in children. I would like to emphasize the importance of timely reauthorization of these laws in order to avoid any disrupting key ongoing and effective programs. We hope to work with Congress to ensure timely passage of legislation that maintains the effective work of these statutes.

Prescription Drug User Fee Act (PDUFA)

FDA's review of new drug applications (NDAs) and biologics license applications (BLAs) is central to FDA's mission to protect and promote the public health. In 1992, Congress enacted PDUFA to speed drug application review, and subsequently has reauthorized it twice.

PDUFA has produced significant benefits for public health, including providing the public access to over 1,200 new drugs and biologics. While maintaining our rigorous review standards, we now review drugs as fast as or faster than anywhere in the world. The median approval time for priority new drug and biologic applications has dropped from 14 months in fiscal year (FY) 1993 to only six months in FY 2006. During the PDUFA era, FDA reviewers have approved approximately:

- 76 new medicines for cancer;
- 178 anti-infective medications (including 56 for treatment of HIV or Hepatitis;
- 111 medicines for metabolic and endocrine disorders;
- 115 medicines for neurological and psychiatric disorders; and
- 80 medicines for cardiovascular and renal disease.

We have complied with provisions of the most recent PDUFA reauthorization directing FDA to consult with the House Committee on Energy and Commerce, the Senate Committee on Health, Education, Labor, and Pensions, and stakeholders in developing recommendations for PDUFA reauthorization. We believe that the Administration's proposal places PDUFA on a sound financial footing, enhances pre-market review, and creates a modern post-market drug safety system that follows products throughout their

full life cycle. Importantly, the proposal also supports new user fees to support the review of direct-to-consumer television advertisements voluntarily submitted to FDA for review prior to airing. We are pleased that the discussion draft is generally consistent with the Administration's recommendations. However, one significant concern to us is the proposal to fund new drug safety activities (outside of those included in the PDUFA proposal) with user fees. In our view the amount that could be raised through user fees could be inadequate to support the new activities. In addition, we are concerned that reopening the PDUFA IV proposal in this manner represents a change in the process for developing user fee programs.

Medical Device User Fee and Modernization Act (MDUFMA)

Similarly, FDA's review of medical device applications is essential to FDA's mission. In 2002, Congress enacted MDUFMA to reduce the time necessary for new medical device application review. As with PDUFA, the medical device user fee program is scheduled to expire on September 30, 2007.

The user fees provided by MDUFMA, and annual appropriations, have allowed us to make significant improvements in the device review program. Since MDUFMA was enacted, FDA has approved more than 150 original PMAs. The following devices intended to address unmet needs in the pediatric population were approved: the first pediatric left-ventricular assist device, a cooling cap to treat severe hypoxic-ischemic encephalopathy in infants, and an expandable prosthetic rib to treat growing children with Thoracic Insufficiency Syndrome.

The device review program also has approved important new laboratory tests, including: the first test for use as an aid in diagnosing West Nile Virus; tests for diabetes management and newborn screening; tests for diagnosing cystic fibrosis; and a rapid screening test for lead poisoning that can be used at health care clinics, mobile health units, and schools.

In the area of women's health, FDA's device review program approved: an optical detection system to identify areas of potential cervical cancer; a non-invasive therapy system to treat uterine fibroids with high-frequency ultrasound; and a clinical laboratory test to determine if a woman with breast cancer is a good candidate for Herceptin therapy. FDA approved other important devices including: the first carotid-stenting systems; a hip resurfacing system intended to treat younger patients who are not ready for hip replacements; and the first over-the-counter automatic external defibrillators.

In preparing our proposed recommendations for MDUFMA reauthorization, as with PDUFA, we have consulted with the House Committee on Energy and Commerce, the Senate Committee on Health, Education, Labor, and Pensions, and stakeholders. We believe our proposal would ensure sound financial footing for the device review program and would enhance the process for pre-market review of device applications. It would change the fee structure of user fees to provide more adequate and stable funding for FDA while maintaining predictability in fees for the medical device industry. Importantly, we also recommend modest modifications to the third party inspection program authorized by MDUFMA that will streamline the program in order to increase participation, while maintaining important safeguards against potential conflicts of

interest. FDA finds significant problems with the existing third party accredited person inspection program, which has garnered minimal industry participation to date. A more robust third party program would permit FDA to focus its resources on establishments and products posing the greatest risk to public health. While we are pleased that much of the discussion draft is consistent with the Administration's proposed recommendations, we are disappointed that these important modifications have not been included. We recommend that these modifications be added to the drafts and note that in the absence of modifications, FDA will continue to expend resources to maintain the program without enhancing its inspectional capabilities.

Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA)

The Administration supports reauthorization of the Best Pharmaceutical for Children's Act (BPCA) and the Pediatric Research Equity Act (PREA) (now called the Pediatric Research Improvement Act [PRIA]). Congress enacted both of these initiatives to promote development of drugs for children because information was inadequate to ensure proper use in children of the majority of drug products approved in the U.S. Together these statutes have transformed information about safety and efficacy for children of important therapeutics and promoted safety and innovation in pediatric drug development. However, we are concerned that the discussion drafts, as presently drafted, contain provisions that could have an unintended and negative impact on these successful programs. I will summarize the successes of these statutes and then comment on certain proposed changes in the discussion draft.

The six-month exclusivity incentives for pediatric studies provided by BPCA has had a powerful impact on providing important, safety, efficacy, and dosing information for drugs used in children. BPCA also expanded and enhanced the initial pediatric exclusivity process by authorizing FDA to establish the Pediatric Advisory Committee (PAC), and provided for post-marketing safety review by PAC of all pediatric products granted exclusivity by FDA. BPCA also promotes transparency by requiring that summaries of the studies conducted under the BPCA be posted regardless of the regulatory action (e.g., approval, non-approval). In addition, BPCA created the Office of Pediatric Therapeutics which, as part of FDA's Office of the Commissioner, provides scientific expertise and ethics advice, and coordinates and facilitates activities that may have any affect on the pediatric population or the practice of pediatric medicine, or may involve pediatric issues.

In contrast to BPCA, which provides a voluntary mechanism for obtaining needed studies on either approved or unapproved indications for a given drug, PREA requires pediatric assessments (based on studies in pediatric populations) of certain drugs and biological products. This requirement is only in the indications that are approved or for which the sponsor is seeking approval, and only under certain circumstances. PREA includes provisions allowing FDA to defer or waive the required pediatric assessments under limited circumstances. As with BPCA, PREA has been successful in generating pediatric studies on many drugs and helping to provide important new information in product labeling.

Together, BPCA and PREA have encouraged the development of important new safety, effectiveness, and dosing information for drugs used in children and led to numerous labeling changes. Since 1997, the exclusivity incentive program has generated labeling changes for 128 products. The labeling changes have significantly increased the information available to health care professionals to use in the treatment of pediatric patients:

- the labeling for 83 products has been updated to include new information expanding use of the product to a broader pediatric population;
- the labeling of 25 products had specific dosing adjustments;
- the labeling of 28 products was changed to show that the products were found **not** to be safe and effective for children; and
- 37 products had new or enhanced pediatric safety information added to the labeling (these numbers add up to a number greater than 128 because some products had more than one change to the labeling).

Since PREA was enacted, there have been approximately 300 applications which have fallen within the scope of the PREA requirements. FDA has approved approximately 40 labeling changes involving pediatric studies linked to PREA assessments since the enactment of the legislation in 2003.

However, the draft legislation contains several provisions that we believe will have a severe negative impact on these successful programs. The BPCA incentive to conduct clinical trials for children will be compromised and the creation of an internal review committee for both BPCA and PREA programs and other program changes will make these successful programs virtually unworkable. For this reason, the Administration

would favor a straight reauthorization over the enactment of these provisions. I will now review some of our specific concerns.

The discussion draft would require FDA, within 180 days, to issue a final rule to establish new criteria to reduce the period of market exclusivity to as low as 3 months, from the 6 months in the current statute. These criteria would include the amount of annual gross sales for all products with the same active moiety as the product, relative to research and development expenses for a requested study. Such a reduction in market exclusivity may be inappropriate because the value of improvements to children's health that may result from better use of drugs is very high. In addition, such a reduction could threaten the willingness of companies to conduct these costly but important trials, thus undermining the success of this program. As mentioned above, the current incentive of the 6 month period of exclusivity has worked well and should be maintained. Through this legislation, FDA has been able to effect important labeling changes on 128 different products. Any weakening of this incentive can only have the effect of reducing its effectiveness. Accordingly, proposals to shorten this incentive or to only provide exclusivity to drugs with one or more year left of patents and exclusivity life are of significant concern.

FDA supports greater internal cooperation; however, the draft bills' creation of an internal review committee for both BPCA and PRIA functions are of concern for a number of reasons. First, a legislative requirement for what are primarily staff functions is in direct conflict with the expertise, flexibility and efficiency needed to ensure rapid

review of pediatric product development. Second, the proposal assigns the dual function of approving written requests and granting exclusivity, which may result in conflicts between the subjective intent of the written request and the objective evaluation as to whether the studies fairly respond to the actual terms of written requests. Third, we believe that tracking pediatric studies are responsibilities more appropriately assigned to agency staff, since they are routine functions that do not require a decision-making body. Overall, these provisions could have the unintended consequence of creating a bottleneck through which all requests must flow and slowing the desired rapid and efficient review of pediatric product development. .

The PRIA discussion draft would require FDA to give priority review status for all supplements to new drug and biologics applications submitted as a result of PRIA. This would remove the flexibility FDA currently has in determining the appropriateness of the priority designation in relation to other priorities. By automatically assigning a preferential priority review to these submissions, that may not be priorities from a public health perspective, many other reviews currently deemed priority on the basis of medical judgment could no longer feasibly be completed within the priority review timeframes.

Finally, BPCA and PREA work in tandem to encourage and require pediatric studies that are vital to the health and welfare of pediatric patients. PREA helps to fill the need for those studies not addressed by BPCA, and we believe that it is important to keep these programs working side by side. Accordingly, we are concerned by the proposal to sunset BPCA, while there is no sunset provision in PRIA. It is important to have a wide

reaching voluntary program balanced with the more limited mandatory studies requirement.

It is critical that programmatic functions not be overburdened with additional requirements that could delay the decisions related to these programs or overburden the drug review system as a whole. FDA wants to build on the success of these programs to help ensure that the best pediatric information is available including critical labeling information that will be of value in treating children.

Pediatric Medical Devices

FDA is committed to supporting the development and availability of safe and effective pediatric medical devices. Designing pediatric medical devices can be challenging. Children are often smaller and more active than adults; body structures and functions change through childhood, and children may be long-term device users—bringing new concerns about device longevity and long-term exposure to implanted materials.

FDA's current initiatives include:

- Recruiting pediatric experts for FDA advisory panels whenever there is a reasonable likelihood that the device under discussion will be used for children;
- Protecting children who participate in clinical trials;
- Collaborating with the Institute of Medicine on the effectiveness of post-market surveillance of pediatric medical devices; and
- Collecting data on the unmet needs for pediatric medical devices and the barriers to the development of new pediatric devices.

However, the discussion draft raises several concerns. The draft would require FDA to track separately the adverse events associated with for-profit sales versus not-for-profit sales of pediatric devices. The public health benefit of such a requirement is unclear, a significant concern for an immensely complicated undertaking that would also represent a major retreat from FDA's recent effort to develop a modern, consolidated system for adverse event tracking.

The draft also would require an annual review of for-profit pediatric devices by the Pediatric Advisory Committee. This duplicative review imposes significant burden without a clear public health benefit.

The draft would also require FDA to cap the quantity of pediatric devices sold for profit and limits the profit making to only those devices indicated solely for pediatric populations, yet many of these devices are used in both adults and children. This approach may thus reduce the availability of safe and effective medical devices for pediatric populations and not provide the intended incentive for further pediatric device development.

Drug Safety

New drugs, biologics, devices, and diagnostics present the greatest opportunities currently available to improve health care and the way medicine is practiced. The number of lives saved that are prolonged by new therapies outweighs the risks that the treatments themselves pose. It is important to remember that no drug is absolutely

without risk and to recognize that sometimes information about the safety of a drug emerges after the drug is on the market. FDA approves a drug only after a sponsor demonstrates that the drug's benefits outweigh its risks for a specific population and a specific indication, and shows that the drug meets the statutory standards for safety and effectiveness. Because of practical limitations on how many patients can be studied for any given drug, the full array of potential risks does not necessarily always emerge during the mandatory clinical trials conducted before approval. Indeed, serious adverse effects may occasionally emerge after approval through post-marketing clinical trials or through spontaneous reporting of adverse events or both.

A robust post-marketing surveillance capacity could dramatically improve our ability to identify such safety issues, and address them before they become serious public health problems. Such a system must rely on both public and private resources and expertise, brought together in public-private partnerships. Such a partnership must have flexibility to assemble analytic and clinical experts and data resources from all sources. Such flexibility will also be crucial to ensure that the system can respond quickly to initiate new targeted safety surveillance in the face of a public health emergency.

However, attempts to address risks must balance access and innovation with regulatory steps to improve the approach to safety issues. Such steps should not impede access to new medical products that can be used safely and effectively by patients suffering from unmet medical needs today. While we want to add requirements when the science of drug safety validates their need, we want to avoid changes that will limit access to new medicines and slow down innovations while doing little to address drug safety.

Therefore, we have a number of key concerns with the bill as presently drafted. In particular, many of the provisions seem fixed on process and structural changes, and not on making fundamental improvements in the science of drug safety. Some changes prescribe specific Agency action when the science of drug safety may not require such intervention, such as the requirement to present all new molecular entities to advisory committees for discussion. Such changes could limit access to needed medicines and slow down new innovations while doing little to address the core issues of drug safety.

We are concerned by the breadth of the proposed requirements for risk evaluation and mitigation strategies outlined in the bill. We believe it is unnecessarily burdensome to require REMS, routine active surveillance and periodic reassessments for all drugs, as the legislation now does. The REMS approach would duplicate and overlap elements of the extensive adverse event reporting system already required by FDA (which includes incident-specific, quarterly, and annual reporting). It would also duplicate existing FDC Act labeling requirements, which provide for MedGuides, package inserts, and other materials which convey information to physicians and pharmacists (as well as patients) to address and minimize risk. Moreover, FDA and industry already engage in efforts with respect to implementation of risk minimization action plans ("RiskMAPs") for those products that warrant such additional risk minimization protocols. In addition, FDA already has authority to require post-approval studies in select circumstances. Codifying new authority is unnecessary.

Finally, the Drug Safety Oversight Board (DSOB) would be used to review disputes between the sponsor and FDA concerning REMS. Not only does the DSOB not have the necessary expertise to handle dispute resolutions, the bill proposes the disputes be raised directly to the DSOB. Since the DSOB would be the primary source of dispute resolution, this requirement would so overburden the DSOB that they will be unable to conduct their other important functions

Improved drug safety is not simply a matter of extending new legal authorities to FDA or requiring the Agency to engage in certain detailed activity. Indeed, extending these interventions or expanding the use of REMS is unlikely to result in improvements in drug safety as desired by the bill's sponsors.

The better overall strategy is to ensure that FDA has appropriate resources and the capacity to develop better scientific tools and approaches to drug review including: (1) improving information available to the Agency; (2) improving the Agency's ability to evaluate this information; and (3) improving how that evaluation is communicated to the public. Accordingly, the Administration's proposed PDUFA IV recommendations support such improvements with respect to:

- the information that the Agency receives, and with which it makes drug-safety related decisions, including the spontaneous reports we get from sponsors and providers as well as our ability to tap into new epidemiological data sets to probe more routine questions;
- our analytical tools and approaches for evaluating the information and turning raw data about drug-safety related questions into practical information that can be

communicated to providers and patients to help them better inform their decision-making; and

- the way in which we can effectively communicate these findings, as well as communicate the Agency's response once we draw a conclusion about the data we have, or are made aware of an emerging drug safety issue.

We also support the addition of provisions for an active drug safety surveillance system that would be established through a public-private partnership and we want to work with you on this provision to ensure the most effective implementation.

FDA actively engages with industry with respect to efforts to implement risk minimization action plans for those products that warrant such additional risk minimization steps. PDUFA IV would provide funds for developing a plan to evaluate current risk management plans and tools. We would obtain input from academia, industry, other government agencies, and other stakeholders regarding the prioritization of the plans and tools to be evaluated. The evaluation would include assessments of the effectiveness of identified RiskMAPS and current risk management and risk communication tools. Based on those evaluations, FDA would conduct an annual systematic review and public discussion of the effectiveness of one or two risk management programs and one major risk management tool. By making such information publicly available we would promote effective and consistent risk management and communication.

Our PDUFA IV proposal includes an increase in funding to improve the information technology (IT) infrastructure for human drug review, to move FDA toward an all-

electronic drug review system. We would use the increased PDUFA IV funds to improve our post-market safety-related IT systems to ensure the best collection, evaluation, and management of the vast quantity of safety data received by FDA. We would use these funds to improve our IT infrastructure to support access to and analyses of externally linked databases, and to enhance FDA's Adverse Event Reporting System and surveillance tools.

Preemption

Finally, we are concerned about new language on preemption in the discussion drafts, which states that nothing in the Act may be construed as having any legal effect on actions for damages under state law (including statutes, regulations, and common law). This language appears in each of the draft bills and relates to both drugs and devices.

With respect to drugs, FDA is the expert federal public health agency charged with ensuring that drugs are safe and effective and that the labeling adequately informs users of the drugs' risks and benefits. FDA reviews the pertinent scientific evidence and, through the drug approval process, provides formal, authoritative conclusions on the conditions under which drugs can be used safely and effectively. This provision in the draft bill could be interpreted to permit state law to undermine FDA's conclusions about drug labeling or about risk evaluation and mitigation strategies. We believe that State law actions that can conflict with the Agency's conclusions and frustrate the Agency's implementation of its public health mandate should not be endorsed in federal laws.

Conclusion

PDUFA III and MDUFMA expire on September 30, 2007, and I want to re-emphasize the importance of achieving a timely reauthorization of these laws. FDA is ready to work with you to accomplish this goal. If we are to sustain our record of accomplishment under PDUFA and MDUFMA, it is critical that these reauthorizations occur seamlessly without any gap between the expiration of the old laws and the enactment of the new ones.

In addition, FDA welcomes the opportunity to work with Congress to ensure that the benefits of the incentive program can continue, in conjunction with FDA's authority to require mandatory studies, as Congress considers the reauthorization of the BPCA and PREA programs.

FDA's mission is to promote and protect the public health. A major component of that mission is to ensure that the American public has access to safe and effective medical products. These statutes are essential to the fulfillment of our mission. We look forward to working with you.

Mr. PALLONE. Thank you. We are going to start with questions and I recognize myself for 5 minutes, Mr. Lutter.

I understand that the administration is in favor of changing the requirement included in our discussion draft that requires all new drugs include a REMS. You would prefer—and again, I am putting words in your mouth, so if you disagree with me at the end here, tell me. But my understanding is that you would prefer that the FDA be granted the discretion to apply REMS when a problem arises with particular drugs as you currently do with RiskMAPs. First let me say, is that correct?

Mr. LUTTER. We are concerned that a broad requirement of REMS being applied to all products may be unnecessary and, in particular, to the allocation of resources to areas where there is no clear public health benefit.

Mr. PALLONE. OK, but then the whole point of the REMS is to mitigate certain unknown risks, but what you seem to be suggesting is that FDA wouldn't react until a risk for a particular drug becomes known, is that correct?

Mr. LUTTER. Well, the purpose of REMS is to mitigate risks, but the concern is that for many products, the need for a particular action beyond what is already in place is not obvious to us and may be unnecessary. That is why we think with the breadth of the requirement on REMS is excessive.

Mr. PALLONE. But why do you think that it is more appropriate to act only when a risk becomes apparent instead of having safeguards in place prior to a risk being revealed? That is what I don't understand.

Mr. LUTTER. Well, the REMS requirement would apply to all products and it may be lifted from all products only if a waiver is granted under circumstances that we think would be very rare if there was a finding of no risk to any sub-populations resulting from use of the waiver. And the real question is whether this process of having REMS applied to all products is one that is efficient and a good use of resources to promote drug safety relative to an alternative one that is more narrowly targeted.

Mr. PALLONE. But how burdensome would this really be on the FDA? Opponents argue that FDA is going to be overwhelmed by REMS requirements, but isn't it true, for most drugs, that the REMS requirements will only consist of labeling and adverse event reporting requirements? Don't new drugs already have to comply with those minimum requirements?

Mr. LUTTER. New drugs do have to comply with those requirements, but we believe that the post-marketing commitments that we are currently to get from industry are generally satisfactory in providing a lot of information to us. We reported, in January 2007, the results of post-marketing studies and in that case, only 3 percent of open post-marketing commitments had been delayed, so in that sense we think our track record is relatively successful in that regard.

Mr. PALLONE. Well, let me get to the post-market safety with regard to medical devices. There is some concern about the lack of attention paid to post-market activities for medical devices. We heard that at the hearing. Specifically, FDA has testified before the subcommittee before that the agency does not feel that a specific

earmark of user fees is necessary because the agency already has the discretion to use the fees that are collected on whatever functions it deems appropriate, whether that be pre-market or post-market. But can you tell me, what kinds of post-market activities are currently being conducted as they relate to medical devices and to what extent those activities are funded by user fees? And how about if you would comment on the idea of annual appropriations, too.

Mr. LUTTER. First, with respect to the amount of user fee money spent on post-marketing safety for devices, I am not aware of that. We can get back to you on that. Overall, the program of medical devices, user fees provides approximately 17 or 18 percent of the medical device program. Our broad point with respect to an earmark is that we believe that the agency management and leadership would benefit from discretion about how to use funds in a most effective way to promote and protect public health pursuant to its mission.

Mr. PALLONE. What about the annual appropriations?

Mr. LUTTER. The specific question there, sir?

Mr. PALLONE. About annual appropriations. We have a provision in the draft to provide for annual appropriations for this purpose. Do you have any comment on that?

Mr. LUTTER. We could always do more with respect to additional appropriations.

Mr. PALLONE. OK. And then lastly, can you tell me, under the authority granted to FDA under section 522 of the Federal Food, Drug and Cosmetic Act, how often does the agency require a manufacturer to conduct post-market studies?

Mr. LUTTER. For drugs or devices, sir?

Mr. PALLONE. For devices. I am only talking about devices now.

Mr. LUTTER. I don't know that. I will have to get back.

Mr. PALLONE. All right, if you could get back to me, I would appreciate it. Thank you. Mr. Deal.

Mr. DEAL. Thank you for being here. Let me ask you about the third party inspection provisions in the draft. First of all, would you explain to us how these third party inspection programs, the changes that are proposed would lead to greater utilization of these inspections?

Mr. LUTTER. The third party inspection program that is in MDUFMA now has not been very extensively used by industry and the key idea in coming up with proposals to improve its use is that it could be used particularly for surveillance, which is essentially routine surveillance. The idea is to what extent should FDA delegate entirely to third parties responsibility for a third party review. With respect to this, the modifications in the third party inspection program for medical devices, those would be intended to promote third party inspections and routine surveillance where we think that is an appropriate use of third party inspection and also, is one that allows our resources to be better allocated for areas of key risk and concern to us.

Mr. DEAL. And my understanding is the proposed changes don't do anything to get rid of safety requirements or conflict of interest provisions.

Mr. LUTTER. That is correct.

Mr. DEAL. And you, as the FDA, could have an inspection on your own at any time you chose?

Mr. LUTTER. We could surely have an inspection on our own in addition to any third party inspection.

Mr. DEAL. Obviously, one of the areas of concern in the proposed preemption provisions that are included in most of these drafts. It is my understanding that there has been a Federal preemption from medical devices since 1976. Is that correct and if so, can you tell us what the purpose of that was?

Mr. LUTTER. My understanding is that there has been exclusive Federal preemption on medical devices for some years. The key purpose of that is, I believe, to ensure consistency in risk communications with respect to devices. One concern that we have with preemption broadly, is that when we make determinations of safety and the effectiveness of products, medical products that we regulate, we would like to be sure that these are communicated in a manner that is clear and understandable to stakeholders, not only patients but also the medical community and the industry, as a whole.

A key concern is that if there are other views, other authoritative views or other dissent of the regulatory requirements, there may instead be a multiplicity of statements about risk, and multiplicity of statements about efficacy which serve, indirectly, to undermine our effectiveness in communicating to the American public about the risks and benefits of medical products that we regulate.

Mr. DEAL. Let me ask you about pediatric drugs. Is the 180 days that is provided from the date of enactment a realistic timeframe for a final rule to be issued on how the tiering of exclusivity would be decided?

Mr. LUTTER. We have a variety of concerns associated with the 180-day deadline and also with that rule, in particular. Issuing that rule within 180 days would be very difficult for us, but the key concern is really the effect of that rule and consideration by FDA, subsequently, of sales relative to the cost of the study on incentives for the industry to develop trials to provide information to patients and healthcare professionals about the benefits and risks to children. We believe that the value of information about the health of kids is so high that it is inappropriate to reduce incentives for these trials and that is why we are concerned about the effect of this rulemaking and its implications for incentives for pediatric trials.

Mr. DEAL. I would like to ask you about the advisory panels and the provisions in the advisory panels that are proposed. First of all, is it difficult to obtain qualified people to serve on advisory panels and as I understand this, the current draft would allow only one waiver per advisory panel for potential conflicts, and what effect would this change have on obtaining the necessary advisory panels and would this have the potential of delaying the effective drugs being put on the market?

Mr. LUTTER. Thank you. We are very concerned about ensuring that the advisory committees that FDA manages operate in a manner that is transparent and clear and enjoys the full trust of the American public. We have taken a variety of steps to strengthen the management of our advisory committees, including in April

2007 we issued a new guidance for public comment that would not only ensure greater transparency and consistency, our use of waivers of conflicts of interest, but also establish new, more stringent criteria for granting waivers of conflicts of interest than are currently required by regulations of the Office of Government Ethics or by existing statute.

That guidance that we issued is now being examined internally. We have received 77 comments from the public about that and we are taking steps to implement it. Broadly, with respect to your question, the concern that we have is that there are so many recognized established scientific experts in the biomedical innovation community who have had financial ties to some sort with affected industry, that it is very difficult to find experts with the authority and the broad recognition of expertise that we want on these committees.

Evidence to this effect is in waivers that I have signed. I sign these waivers for the Food and Drug Administration. They are posted on our Web site and in a collection of recent ones, you will see this waiver is signed after we have looked for a collection of experts at the National Institute of Health and within FDA. We are signing these after deliberate efforts to search for appropriate expertise from unconflicted individuals and then found that we were unable to find the expertise that we needed.

Mr. DEAL. Thank you.

Mr. PALLONE. Thank you. Mrs. Capps.

Mrs. CAPPS. Thank you, Mr. Chairman. Dr. Lutter, Avandia was a wildly successful drug when it came onto the market. Since being introduced in 1999 it has blossomed into a $3.2 billion per year drug. However, with this success, information of its shortcomings has come to surface. Specifically, its association with increased risk of heart attacks among people with diabetes, a population already at higher risk for heart disease. I applaud the FDA for convening an advisory committee hearing scheduled now for July 30 on Avandia.

I have two questions to ask you about this, briefly, if you would answer. One, how did your agency advertise for positions on this advisory committee?

Mr. LUTTER. The advisory committee is comprised with requirements under the Federal Advisory Committees Act as a collection of standing members who serve 4-year terms and are appointed for a 4-year term in anticipation of whatever events may arise during those 4 years. So in that sense, those standing members who will serve on that panel have been appointed in the past. We have greatly improved our process for recruiting members of all advisory committees. In February of this year we posted on our Web site a centralized listing of all vacancies so that an expert in rheumatology or pediatric rheumatology or cardiology with interest in serving on different committees or one committee at FDA doesn't need to track down which of our 47 panels might have a vacancy, but instead can submit his or her resume or nomination to a single source and thereby we can review that application in an integrated manner.

Mrs. CAPPS. Let me try it this way. Do you anticipate any members of this advisory committee having any conflicts of interest with this particular hearing that you have scheduled?

Mr. LUTTER. At this point? It is too early to say. We have a process which involves extensive review of all the financial holdings of all members of the advisory committees. That process takes approximately 45 to 60 days, even when it is done on a very accelerated basis.

Mrs. CAPPS. Is that ongoing now?

Mr. LUTTER. Yes, it is ongoing.

Mrs. CAPPS. Will you complete it by the time of the hearing?

Mr. LUTTER. Absolutely.

Mrs. CAPPS. So you will know how many people, but you can't say it now?

Mr. LUTTER. It is not completed.

Mrs. CAPPS. And they will serve whether or not they have a conflict of interest?

Mr. LUTTER. We will review their qualifications. We will review their qualifications with respect to the statutory requirement, which is if the need for their expertise outweigh the potential conflicts of interest, we will grant waivers accordingly and in a manner consistent with the statute and also the guidance that we have currently in place.

Mrs. CAPPS. So you might not allow some of the advisory members to serve on this panel?

Mr. LUTTER. As a routine matter, we occasionally decide that different candidates who may be considered for panels are not appropriate because of conflicts of interest.

Mrs. CAPPS. And then they don't serve?

Mr. LUTTER. They recuse themselves, we recuse them or we may limit their participation based on the findings.

Mrs. CAPPS. And this is a matter of public record, those that have been asked on different panels so that when your hearing is scheduled the public will know which members have been asked not to serve——

Mr. LUTTER. For reasons of privacy, we do not reveal the different reasons that they have not——

Mrs. CAPPS. But you do acknowledge which ones are not serving who are regularly on the committee?

Mr. LUTTER. Well, the names of everybody on the committee is a matter of public record and the participants in the meeting is also a matter of public record.

Mrs. CAPPS. Thank you. I want to ask you another question, though I am not particularly satisfied there. Maybe there will be a way to communicate in writing with some additional questions about this process.

Mr. PALLONE. The members may ask additional questions in writing, certainly.

Mrs. CAPPS. Thank you. Let me get one more topic on this particular drug out and you may not have time to answer me now, but I would like that answer in writing, too. A New York Times article published yesterday the story of Dr. Johann-Liang. She joined the FDA in 2000 and eventually rose to deputy division director in the agency's Office of Surveillance and Epidemiology. However, soon

after she recommended a black box warning for Avandia over a year ago, things changed. She became increasingly excluded from important reviews and meetings and eventually, she left your agency. That is what the article in the New York Times reported. My question is: after she made her conclusion regarding Avandia's heart risk, was she increasingly supervised by her FDA supervisors? Please answer yes or no.

Mr. LUTTER. I am sorry, I don't have enough information to answer.

Mrs. CAPPS. Is there a way you can find out?

Mr. LUTTER. We can back to you on that.

Mrs. CAPPS. I would like that in writing, then, since you don't know today. I do think this case illustrates a larger problem at FDA of employee morale and political interference in scientific decision making. I think it is hard for us, in this case, not to draw some kind of connection between industry influence and an incident like this. I yield back my time.

Mr. PALLONE. Thank you. Mr. Ferguson.

Mr. FERGUSON. Thank you, Mr. Chairman. Thank you, Dr. Lutter, for being here, as well. I just want to begin by echoing some of the concerns that Mr. Deal and Mr. Rogers had raised before. I know, from being on the other side in this committee and subcommittee, the best work that we do is work that is thorough and frankly, takes into account lots of different viewpoints and the work that we have done over the years in a bipartisan fashion, that has always been the spirit of this committee and I think that has largely been the case with regard to the legislation that we are considering today.

It has perhaps not been as much the case the last several days. And I am hopeful that in the next several days and in weeks ahead, as we work through this legislation, that we really will be able to take more viewpoints into account. I have a particular concern, I have several concerns about the legislation that we are looking at.

One in particular is preemption language that Mr. Deal had raised before. I think Mr. Rogers made a very eloquent, brief case for an alternative point of view than is reflected in the draft, the drafts that we are looking at and I think, my sense is that having something dropped into a draft mysteriously at the last second, I know from it happening some time when I was in the majority. It never serves the civility and a solid end product very well on this committee and I am hopeful that we can address that in the next several days.

Dr. Lutter, as you know, the FDA is currently holding a public meeting on medication guides today and tomorrow. Just a couple of hours ago I actually testified at that hearing and at that public meeting. I presented, just this morning, the findings of a year-long investigation that we had been conducting in my office about the distribution of medication guides and I want to register my thanks to you and to the FDA and the agency for holding the public hearing and focusing on the issue. As I said, at the public meeting this morning, and I repeated at the committee hearings here, the current regulation of medication guides represents a potentially alarming situation in which young patients and their parents may

not be receiving the information they need to make fully informed decisions about certain prescription medications.

It is clearly all of our shared goal to ensure that patients, including children, have the access to the safest and most effective therapies. But taking that into consideration, the FDA has rightly implemented strict requirements on the prescribing of some drugs, including antidepressants used by children and adolescents by issuing black box warnings and requiring medication guides. Those and other requirements are necessary to ensure that people to whom certain medications are prescribed, including parents and adolescents, parents of children and adolescents have the information they need to make fully formed decisions.

If these needed requirements are not being implemented, the public can't make fully informed decisions and therefore may be placed at risk and that may well be that in many cases, the children and adolescents who are being prescribed these particular drugs may be receiving the medication guides, but it can't be said with certainty at a hundred percent of the time these parents are receiving this information. There has been a breakdown in the communication between the FDA and State boards of pharmacy. The FDA issues the regulations on med guides. State boards of pharmacy are charged with enforcing the regulations on the distribution of medication guides.

And I have been in correspondence back and forth with our New Jersey State Board of Pharmacy and with the FDA and others. I believe that one component to a solution to this problem that we face is communication, consistent dialog between the FDA and the National Association of Boards of Pharmacy. I think that can be a very helpful part of this process.

Dr. Lutter, does the FDA currently have the ability and the authority to work with groups like these to keep them fully updated on the ever-changing duties regarding the distribution of medication guides?

Mr. LUTTER. We work very closely with the National Association of Boards of Pharmacy and with State boards of pharmacy in different States and I appreciate very much your interest in our public meeting on medication guides this morning. As you know, several members of the senior leaders of the team spoke there and I was looking forward, myself, to the opportunity but decided I would better spend my time preparing here.

With respect to the broad question, though, we are very concerned about ensuring that information about the risks of pharmaceutical products is conveyed as effectively as possible to patients, to their families and to their healthcare providers. In that sense, this public meeting that we are holding today is an open, transparent, visible and we are grateful for our participation. We are thankful for the different participation of the various stakeholders and we will work expeditiously to ensure that medication guides provide as effective communication of risk as possible in the future.

Mr. FERGUSON. Thank you for that. I know the FDA has been engaged with pharmacist organizations and others about the distribution chain of medication guides. But it is my understanding, my sense, really, that the FDA has dragged its feet a little bit on enabling pharmacists to provide and produce medication guides elec-

tronically. Don't you think it makes sense to give pharmacists the ability to electronically print out med guides to alleviate the problems that may be currently in the med guide chain? I mean, one concern we hear from pharmacists all the time is they simply don't have the shelf space to store boxes and boxes and boxes of paper medication guides. We allow them to distribute other things electronically, just print them out at the pharmacy. Is it your sense that it would also make sense to allow them to do this?

Mr. LUTTER. I think that is one potentially very intriguing option that we will explore in the course of looking at all public comments received in the course of the public meeting on medication guides today.

Mr. FERGUSON. As you might guess, I am a strong supporter of electronic distribution of med guides. I just think it doesn't sacrifice the quality of information, but enhances the quantity of information that is available, particularly to parents, as they are trying to—and the great thing about medication guides, as you well know, is it is in English. A non-doctor, non-pharmacist can actually read it, understand it and therefore make a more informed better decision about the healthcare of their child. I would ask my colleagues on the committee to consider changes, as we work through this legislation and reauthorization, that would encourage or mandate the FDA to engage in these measures, to use some of these measures to streamline or enhance the distribution of medication guides. I think it would do a great deal to help the cause of public health and in addition to some of the other concerns and issues that I raise, Mr. Chairman, that would help to get to work through as we mark up and move this legislation, I hope that this might be something that we could consider, as well, and I yield back.

Mr. PALLONE. Thank you. Ms. DeGette.

Ms. DEGETTE. Thank you, Mr. Chairman. Dr. Lutter, recently Dr. Shuren, who is here, I see, testified before this subcommittee and I had a whole series of questions for him about medical devices in pediatric populations which we forwarded to the FDA but which we have not received written responses back to yet, so I thought I would ask you these questions. The first one is that the Institute of Medicine conducted a study to determine whether the FDA's system for post-market surveillance of medical devices provides adequate safeguards for their use in pediatric populations. The study included a number of recommendations for the FDA and I will enumerate them quickly.

Number 1, collaboration with the National Institutes of Health and the Agency for Healthcare Research and Quality to define a research agenda and priorities for the evaluation of short and long-term safety and effectiveness of medical device use with growing and developing children.

Number 2, promotion of the development and use of standards and approaches for capturing and linking use and outcomes data for medical devices.

Number 3, collaboration with industry, healthcare professionals and organizations and parent and patient advocates to improve adverse event reporting.

Number 4, oversight of the management of high profile medical device safety issues similar to the independent drug safety over-

sight board within the FDA and finally, establishment of a central point of responsibility where pediatric issues within the Center for Devices and Radiological Health to evaluate the adequacy of the center's use of pediatric expertise and its attention to pediatric issues in all aspects of its work. That is a long list, but I want to have it in the record because I want to ask you whether the FDA has adopted any of those recommendations.

Mr. LUTTER. We are in the process of reviewing both your letter and the recommendations and I am not prepared to give you a more explicit answer on that. I don't know.

Ms. DEGETTE. So you don't know whether they have adopted those recommendations?

Mr. LUTTER. I understand you sent this letter and we owe you a reply and I look forward——

Ms. DEGETTE. Well, but the recommendations were made before I sent the letter and now you guys have had over a month to review the letter and the previously made recommendations, so have you all implemented any of them?

Mr. LUTTER. I am not informed about the status of this. We will have to get back to——

Ms. DEGETTE. Did you know about my letter before today's hearing?

Mr. LUTTER. No, I didn't.

Ms. DEGETTE. When did you find out about it?

Mr. LUTTER. This letter and the specific contents I am learning about now.

Ms. DEGETTE. You didn't know about my letter until I asked you the question just now?

Mr. LUTTER. I didn't know about the contents until you asked me the questions.

Ms. DEGETTE. OK. Mr. Chairman, I would ask unanimous consent for a written response to my letter, which was made after the last hearing within 2 weeks of today's date.

Mr. PALLONE. Without objection, so ordered.

Ms. DEGETTE. Thank you.

Mr. PALLONE. I would hope that you would be able to do that.

Ms. DEGETTE. And especially since your staff is sitting right here in this room who were at the hearing last week. Now, there were also a number of recommendations in this report; you probably don't know about these, either, but I will put them on the record. They cited recommendations for Congress, including, No. 1, requiring the FDA to establish a system for monitoring and publicly reporting the status of post-market study commitments involving medical devices.

Number 2, permitting the FDA to order post-market studies as a condition of clearance for the categories of devices for which section 522 post-market surveillance studies are now allowed, and No. 3, allowing the FDA to extend those studies for devices with expected high pediatric use beyond the current 3-year limit.

Do you think that Congress should follow these recommendations and make those necessary statutory changes?

Mr. LUTTER. Could I ask you to repeat the question?

Ms. DEGETTE. You bet. The same report I just referred to cited a number of recommendations for Congress requiring the FDA es-

tablish a system for monitoring and publicly reporting the status of post-market study commitments involving medical devices, permitting the FDA to order post-market studies as a condition for clearance for the categories of devices for which section 522 post-market surveillance studies are now allowed and No. 3, allowing the FDA to extend those studies for devices with expected high pediatric use beyond the 3-year limit. Do you think those are good ideas?

Mr. LUTTER. Now, with respect to the first one on the monitoring and reporting of post-marketing studies, we think we already have some ongoing programs in that regard, but ma'am, these are really areas where I need to express my apologies and say that I am not in a position to respond about the specific program and I will have to get back to you on this.

Ms. DEGETTE. OK. This was a study that was conducted by the Institute of Medicine. Oh, it came out in 2005, so I would appreciate it if you would have your staff review those recommendations and also get back to me in writing.

In April, Dr. Theresa Mullin, who is also here in this room, testified before this committee. I asked her, given the public's loss of faith in the FDA's ability to regulate the drug industry whether it would be possible to hold the next round of PDUFA negotiations in public and I also asked whether commercial, confidential or trade secret material of individual companies was discussed at those meetings. Dr. Mullin said to me there is no confidential, commercial, trade secret, anything of that type discussed in such meetings. So I would just like to confirm, does the FDA have any concern over opening up the PDUFA negotiation process to the public since none of these confidential things are discussed in the meetings?

Mr. LUTTER. Let me offer a brief comment on background before I offer the specific answer to your question. We think that the process would run with respect to developing our PDUFA recommendations has already complied with not only the statutory requirements for involving all stakeholders, but is exemplary in that it had a public meeting a year ago last fall; it had another public meeting more recently and it had a series of approximately a half dozen meeting with public interest groups, stakeholders like patient representatives and consumer representatives, as well as the healthcare provider community.

In that sense, there has already been, we believe, ample input from non-industry participants in this process. If these participants, these stakeholders wanted to sit in on the meetings, this is something that may raise challenges from the viewpoint of efficient use of time and the detailed nature of these discussions, but it is not something that we have any particular objections to.

Ms. DEGETTE. OK. There are a number of provisions included in these bills that address direct-to-consumer advertising from drug companies. In the PDUFA legislation we are talking about, drug companies may pay a user fee to submit to direct-to-consumer television advertisements for advisory review. So given that it is a voluntary program, I am wondering how beneficial it will be and quickly, could you answer for me what percentage of direct-to-consumer television advertisements are reviewed by the FDA?

Mr. LUTTER. I don't know that answer, but I do know that in developing that proposal, we paid a lot of attention to how much work would be involved and the specific answer was that we expected approximately 150 television ads to come in for review and this suggests that it is a large number that would offer significant benefits to the American public in terms of ensuring that a large set of TV advertisements meet appropriate standards are truthful and not misleading.

Ms. DEGETTE. Again, Mr. Chairman, I guess in the same answer that I am going to get in 2 weeks, if you could provide the information I have asked for, what percentage of these television advertisements are reviewed. I would appreciate it. Thank you.

Mr. PALLONE. Thank you. You heard our requests. If we can get this back in writing within 2 weeks, we would appreciate it.

Mr. LUTTER. We understand, thank you.

Mr. PALLONE. Thank you. Mrs. Wilson.

Mrs. WILSON. Thank you, Mr. Chairman, and thank you very much for being here. I think there is a generalized agreement that we need to do more with respect to post-market surveillance of drugs and side effects and so forth. Can you explain how that might be achieved and what your views are on how we can modernize our drug safety system with respect to post-market surveillance. The draft of the legislation, I think, is fairly general, but what do we need to do to strengthen post-market surveillance and how might you implement that?

Mr. LUTTER. The draft and language in Senate proposals emphasized, at one point, or mentioned at one point, something that we think would be fair to emphasize and that is a public/private partnership on surveillance. And the idea is that FDA and perhaps the Reagan-Udall Institute, which was outlined in some detail in the Senate provision, could work with a very broad collection of private parties to ensure that appropriate expertise is brought to bear about statistical data mining, signal detection, signal characterization and through the interlinking of different databases using electronic medical records and other new information technology systems.

This is not something that may be done successfully overnight, but it is a vision of what would be the future of drug safety. It is something that we announced in a public meeting earlier this year, called the Sentinel Network. I think we held that in February and we are working with a variety of stakeholders inside and outside the Government to try and cooperate in the interlinking of electronic databases. We believe that further language in the discussion draft characterizing this public/private partnership, linking it, in particular, to the Reagan-Udall Foundation might be beneficial.

Mrs. WILSON. How would it really work? And I am quite familiar with linking databases and doing statistical analysis and so forth, but as a regulator, how would this work and change either the information that is available to consumers or families, or change your regulatory approach to now how are you going to decide that a drug should be taken off the market or a special warning needs to be put on a drug?

Mr. LUTTER. Such a partnership and the system of interlinked databases would not change our regulatory standards, the stand-

ards for making regulatory decisions would be independent of that. But what it would do is give us substantially new, more and better, more timely information about risks and in particular, if these databases existed and could be analyzed more quickly than we now are able to do with the post-market surveillance system currently in place, we would be better able to detect signals about adverse events like heart attacks or heart failure and we would thereby have an ability to inform families, patients and doctors earlier about these risks through label changes, through black box warnings. It might be implemented earlier than would otherwise be the case and that is the way in which it would matter to families.

Mrs. WILSON. Let me ask you something about device recalls. When a medical device recall is issued, to whom is it issued and can the FDA currently direct a company to notify patients about a recall or do you need more specific legislative language in order to direct them to do so?

Mr. LUTTER. Device recalls fall into several categories, depending on their class and depending on the level of information about the health risks and we do not, at this point, my understanding is that we do not have information to notify individual patients. We are working expeditiously on the development of a unique device identifier that may provide more information and a better way of communicating concerns to families.

Mrs. WILSON. But do you have the authority that you need to direct a company to inform patients currently or is greater authority required?

Mr. LUTTER. Yes, we currently have authority to notify patients.

Mrs. WILSON. To notify patients or direct that companies notify patients?

Mr. LUTTER. We have authority to do both.

Mrs. WILSON. OK. Thank you. That is all I have, Mr. Chairman.

Mr. PALLONE. Thank you. The gentlewoman from Oregon.

Ms. HOOLEY. Thank you, Mr. Chairman. Dr. Lutter, I have been working with Mr. Engel and Mrs. Capps with pharmaceutical groups to help address the concerns about pharmacy compounding. I believe that traditional pharmacy compounding provides an extremely valuable service to consumers. It enables patients to get the medicines they need that would otherwise have been unavailable. However, I have been concerned about a couple of recent events that have happened in my State where two people in Portland and one in Washington State died because of a pharmacy compounding mistake.

I believe we need to ensure patients know they are taking a compounded drug, but we must do so without unduly burdening pharmacists. Do you believe the FDA and the State Board of Pharmacy have all the tools they need to ensure pharmacy compounding is done safely? Or what do you need?

Mr. LUTTER. Currently we are concerned about the safety of patients and of compounded drugs. We have taken a variety of enforcement actions against pharmacy compounders who may be making products that are unsafe through a very large industrial level, organizations and manufacture of products and we have taken enforcement action against those. As you know, there is pending litigation on compounding and we look forward to the out-

come of that. But with respect to our efforts currently to ensure that safety of the American public and of patients from compounding drugs, we are currently taking enforcement action and since this is where we believe that compounders are violating the law.

Ms. HOOLEY. You have small pharmacists that make a few compounds because that is what the patients need and then you have large companies doing compounding. Do you distinguish between the two? Do you need further authority to make a difference here?

Mr. LUTTER. The distinction is nuance. It depends on whether or not the products are being made by the pharmacist in response to a prescription written by an authorized healthcare provider for an individual patient and in that instance, it is an area which falls into traditional compounding and does not merit further new authorities on our part. We have authorities to take action against compounders who are essentially producing unapproved drugs because they are working on an industrial type of operation, and in instances where we find that there are products that are unsafe for the American public being sold by such compounders, we do take such action.

Mr. PALLONE. The gentlewoman is done. Mr. Burgess.

Mr. BURGESS. Yes. Doctor, let me just follow up on that briefly about the compounding issue. How do those compounding issues come to your attention if there is a small pharmacy that is compounding a particular medication, how does that come to the FDA's attention? Why type of surveillance do you have over the small pharmacy that is providing that service for patients?

Mr. LUTTER. Well, we have a very large collection of ways of getting information. It may be other pharmacists, it may be drug companies, it may be healthcare providers, it may be patients, it may be the State Boards of Pharmacy, sort of a variety it may come from and it would really depend on the individual circumstance.

Mr. BURGESS. But there is not a structured surveillance system at the FDA that oversees that?

Mr. LUTTER. We have an adverse event reporting for all drugs and I am not familiar with whether or not it has any information organized in it about compounded products as opposed to non-compounded products.

Mr. BURGESS. OK, thank you. Under the negotiation process for PDUFA IV, you said in your testimony you met with the various stakeholders. Were you meeting with patient groups during that time, as well?

Mr. LUTTER. Absolutely. The stakeholders included patient representatives, consumer representatives and representatives of medical organizations such as pharmacists.

Mr. BURGESS. Now, in the brief time that I have had, that my staff has had the ability to have the bill, there are some technical problems with the drafts. Has the other side, the majority, afforded you the opportunity to provide technical comments on the drafts as they have been submitted?

Mr. LUTTER. We met with staff last week. We received the bill last Thursday. We look forward very much to further opportunities to meet with staff over the next few days and weeks.

Mr. BURGESS. And are those discussions, are those generally available to the staff on both sides of the dais?

Mr. LUTTER. Absolutely.

Mr. BURGESS. OK. I also want to ask a question about the New York Times article yesterday. We have already heard that referenced at one point. Now, prior to PDUFA—I am a physician and practiced in the 1980s. I do remember the slow pace of new drug approvals and it was painful and I think it was a group of, actually, AIDS activists who said look, we are being denied significant medication that could help us because of the length of time it takes the FDA to approve medication, so the need for speed was certainly underlined in the early 1990's when a Democratic Congress passed the first version of PDUFA. Now we are in discussions that perhaps we are approving things too quickly, that safety needs to balance the speed. How good a job are we doing at balancing safety and speed under our present system?

Mr. LUTTER. A key point to recognize is that PDUFA gives FDA more resources and in that sense, the dichotomy that has often been described, that is between access and safety is false. It suggests that without additional resources and without the additional staff and information technology support that PDUFA fees can provide, we are unable to do things better in the same amount of time. In fact, we can. And the whole thesis behind the success of reauthorizations of PDUFA ever since 1992 is that with the additional resources we are able to review, not approve, but to review product applications faster, in a manner that preserves our ability to ensure that they meet exactly the same standards that existed prior to PDUFA.

And in that sense, the strength of the statute has really been through additional resources. We have an ability to make review decisions which tend to be associated with approval decisions and therefore access, but from our perspective, they are review decisions, be they approval or non-approval, faster. As a result, we are able to lead to faster access of drugs to market in a way that promotes the access that was driving the AIDS activists about 20 years ago in a manner that benefits the American public and does not sacrifice, in our judgment, drug safety at all.

Mr. BURGESS. And then, just in the brief time I have left, would you address again for me, if you would, the issue of conflict of interests, the need for having the technical expertise to have the experts in the room. When you were answering the question earlier, I guess I was left with a question in my mind, who sort of oversees that process? Who oversees the overseer in that regard? How can we know that you did have the right experts in the room, that they weren't excluded because of a perceived conflict of interest, or on the other hand, how do we know that a conflict of interest was not allowed to have access to the decision making process where it really would have been inappropriate?

Mr. LUTTER. Well, with respect to who oversees the overseer within FDA, I do. I sign the waivers of conflicts of interest and under my jurisdiction is the Advisory Committee Oversight and Management Staff. More broadly, the public and you. We post on our Web site all of the waivers that we are permitted to under law. We post, also, information disclosures signed by the advisory com-

mittees, themselves. We reveal to the public, during the advisory committee meetings, the conflicts of interest that may be present by the advisory committee members or consultants that we bring to the advisory committee meetings. All of this is available to the public and in that sense, we operate under a regime of full disclosure to the extent that any conflicts are revealed that are material. We disclose them to the public through the advisory committee meetings, themselves, and on the Web site.

Mr. BURGESS. But if I could just interrupt and how do we ensure that the balance doesn't go too far the other way? Maybe I will submit that to you in writing because that is a concern of mine. Thank you for your time.

Mr. PALLONE. Thank you. Ms. Eshoo.

Ms. ESHOO. Thank you for recognizing me, Mr. Chairman. Thank you, Doctor, for your testimony. First, I just want to make a comment about this direct-to-consumer advertising. I don't like any advertising of pharmaceutical companies. I just don't find it to be appropriate and the idea that this is really in-depth information to consumers, I think is a joke. I mean, it is on par with political advertising. I mean, how much do you know about a candidate in 30 seconds or less? So I just don't like it and I think that the way it is set up, that the program is almost designed to fail because companies don't have to submit their DTC ads for review and they don't have to pay fees to support the program. I don't know. At any rate, every time I hear about advertising, it really pushes a button with me. Here are my questions.

On third party inspections, when we authorized MDUFMA in 2002, we actually, with reluctance, established a third party inspection program. It was controversial and the legislation was not easy to get done. In fact, I think most bets were that it would fail. But I think that we have taken some very large important steps forward and I am proud of it, I am pleased about it. Now, the purpose of the program was to allow the agency to have some resources, obviously, to utilize outside accredited inspectors to conduct the inspections and provide reports back to the FDA. Now, the GAO report published earlier this year found that manufacturers have been reluctant to participate in the program because of the number of statutory obstacles. First, what has FDA done to increase the participation in the third party program and has the agency done anything since its inception to increase the number of inspections actually conducted by FDA? And do you agree with the GAO findings?

I don't have a lot of time. I have some other questions.

Mr. LUTTER. We will have to get back to you on that.

Ms. ESHOO. That is interesting. Good, I will look forward to hearing back from you. I have serious concerns about liberalizing the third party program. The reliance on third party has always had, as I said earlier in my opening statement, a real push and pull to it. While I think it has worked, I think the public has raised legitimate questions about it and it can be likened to the fox being in charge of the chicken coop, although I think that that diminishes some of the things that happen, there is that kind of take on it.

Now, I understand that the industry is frustrated by the lack of direct oversight conducted by the FDA and so the third party pro-

gram ends up being a good alternative for them. Do you think that this is set up so that it lessens the FDA's inspection authority under the law? It relates back to what I was asking before and you said you have to get back to me, but I want to probe in this area to see how far we have come since the 2002 legislation became law.

Mr. LUTTER. We believe that with the recommendations for change in our MDUFMA proposal, it would not lessen at all the FDA's authority. The key question is efficient use of resources that we have and an ability to allocate them with respect to risks that we believe are important. What we have is a proposal for a third party——

Ms. ESHOO. But the participation, historically, has been low, so I am asking you what you think has worked, that the proposed legislation really enhances, the best of what we made law in 2002. There is something not working right because the participation is low.

Mr. LUTTER. We agree that the program currently has not worked. We agree with you.

Ms. ESHOO. Now, why? Why do you think so, FDA? GAO has leaned in on it. Why do you think it hasn't?

Mr. LUTTER. We think it is partly for the lack of the changes that we are making with respect to the particular——

Ms. ESHOO. Did you ever come up and ask for additional authorities or changes in this?

Mr. LUTTER. Well, the changes are ones that we are now asking for with respect to part of the MDUFMA proposal. The key concern that we have is the use of resources internally. We have spent, I think it is like $3 million over the years as part of MDUFMA, implementing the proposal. It is very little money for third party inspection and, that is, the use of our resources that aren't well spent relative to alternative ways of improving device safety.

Ms. ESHOO. Can I just get a real quick one in here regarding the sunset of PREA and the exclusivity incentive under the BPCA? Does the FDA prefer any of the provisions that are being cast about, the blockbuster provision included in the Committee Print or an extension of the 6-month exclusivity?

Mr. LUTTER. We would prefer the existing statute for its simplicity and for the high incentives that it gives for pediatric trials that provide information that benefit the children.

Ms. ESHOO. Thank you. Thank you, Mr. Chairman.

Mr. PALLONE. Thank you. I didn't know what your intention was there with the other gentleman and if you wanted to have one of them answer a question, that is fine. I didn't know if that is what you were trying to do there.

Mr. LUTTER. Thank you, sir. We will figure it out.

Mr. PALLONE. All right. Mr. Pitts.

Mr. PITTS. Thank you, Mr. Chairman. To follow up, just briefly on Congresswoman Wilson's question about, Dr. Lutter, has the agency done anything to date related to establishing a unique device identifier system for medical devices?

Mr. LUTTER. We are currently involved in a rulemaking process that would allow for the development of unique device identifiers and we are pursuing that expeditiously.

Mr. PITTS. Now, some claim it is not as easy to establish a UDI system for devices as it is for drugs. Can you please explain what issues make UDI for devices more complicated along with the steps that you are proposing to address those concerns?

Mr. LUTTER. I am not in a position at this time to talk about the rulemaking that is ongoing. I think with respect to the difficulties, the first question is that unlike with the drugs, there is a threshold issue of scope. Is it all medical devices or is it only a subset and what is the subset of special concern; is it implantable or does it go more broadly than that. And second, there is also a question of how the unique device identifiers should be linked to the device, itself; is it on the labeling or should it be implanted in some way on the device so that it can't be separated, even after the device is separated from its labeling. Those are questions that we will consider in the rulemaking.

Mr. PITTS. Regarding preemption, some proponents of the labeling or language, claimed that the language only has to do with provisions in the current bills before us. Would it not be counterproductive to public health for States to impose different REMS requirements than those imposed by the FDA?

Mr. LUTTER. Confusion about REMS requirements or confusion about risks of FDA-regulated products is broadly of concern to us because it undermines both the trust that we need to have with the public to communicate the risk with them in a manner that lets them take appropriate action to control and to mitigate those risks and we think that preemption language would essentially have the effect of formalizing, in Federal statute, a collection of State actions that may be contradictory to or inconsistent with FDA actions on the safety and effectiveness of FDA-regulated products.

Mr. PITTS. That is all I have. Thank you, Mr. Chairman.

Mr. PALLONE. The gentleman from Utah.

Mr. MATHESON. Mr. Chairman, I have a series of questions I am going to submit in writing. I am not, after discussion with the agency, I am pretty sure they are not ready to answer today, so I will just submit them for written response. I yield back.

Mr. PALLONE. Thank you. Mr. Rogers. He is not there? Mr. Buyer.

Mr. BUYER. Thank you. I would like to follow-up on Mr. Pitts' questions. If all this legislation is intended to strengthen your ability to give assurances to the public about the products that are in the marketplace, how is it that the provisions that are in the bill regarding preemption actually allow you to do that? If we are going to allow these State class action lawsuits to even make jurisprudence more complex, how does that help you do your job?

Mr. LUTTER. We are concerned with the preemption provision in the discussion draft, because it may actually complicate our efforts to communicate risks in a manner that people understand. And the key question is, if we have additional resources through PDUFA and an additional set of information about risk, do we also have a system that we can convey to the public the risks of and the benefits of use in FDA-regulated products? We think that the preemption position may undermine our ability to do that effectively by allowing for multiplicity of views in State jurisdictions that may be

seen as contrary to or inconsistent with the FDA statements about risks and effectiveness.

Mr. BUYER. Mr. Pitts asked you about unique device identifiers. Let us talk about your present authority as opposed to what authority you may not have that you may need for us to put in a bill. Right now you have authority to require tracking for class II and class III devices, correct?

Mr. LUTTER. Yes.

Mr. BUYER. Now, in the bill, it appears that there is a broad expansion, which would require unique device identifiers on about anything imaginable that we are going to put into the body. Now, you said you don't want to talk about your present rulemaking on the development of a present system, but it would be shocking to me that the FDA would like to create a system in a rulemaking whereby you would have—well, let me take another step back. I would think that you need to create a rule that would have tracking orders that would be issued based on risk, would it not?

Mr. LUTTER. Our focus, in general, in managing the agency is on risk and we try to be——

Mr. BUYER. So earlier, when you talked about scope and subsets of scope, you are talking about tracking devices that are going to go into the body based on the risk and the impact that failure could have, right?

Mr. LUTTER. That is correct.

Mr. BUYER. So when we want you to have that focus in that scope, how does broadening the expansion to apply to about every device imaginable going into the body help you do your job if tracking is not going to be based on assessment of the risk?

Mr. LUTTER. In general, our effort and our policy with respect to protecting and promoting public health is to emphasize the risks of greatest concern and in that sense we would be concerned about excess breadth in the design of a program to focus unique identifiers. With respect to the particular language, this is something that because we received this only last Thursday, we should probably welcome that opportunity to talk separately with your staff about the unique identifier language, because this is not an area that we have studied in this legislation in detail.

Mr. BUYER. As you are developing your regulations for your own type of tracking system, what is your timeline to complete such system?

Mr. LUTTER. We are committed to doing it expeditiously, but we do not have a timeline for completion of a final rulemaking.

Mr. BUYER. Would your counsel to us be for you to complete your work and for us to then provide the oversight with regard to your system? And then, if we have questions or have our own ideas or want to broaden its scope, it would be more prudent to modify FDA's system rather than Congress just mandating a broad expansion with no regard to the system you are presently developing?

Mr. LUTTER. Well, the present program is one that we are developing without any concern about limitations of authorities in regard. So in that sense it is one that we think is worth pursuing with existing authorities, yes.

Mr. BUYER. Yes. In other hearings FDA had witnesses come before us, and not only myself but some other members of the com-

mittee have been concerned about counterfeit drugs and their prevalence in the marketplace. So we have seen this growth of adverse events reports over the last 3 years, and I have been trying to figure out what has been the impact of the growing prevalence of counterfeit drugs on the marketplace on this increase in adverse reports. What I am learning is that it is very difficult to determine this impact, and that, really, the system itself is not set in such a manner whereby we can have such retrospective analysis of that data. So I have a couple of recommendations that you can do on your own that we don't have to put into law, so I want you to please take these back to the FDA, and I think we can be helpful to each other.

What I am learning also, from the current MedWatch adverse events reporting, on the reporting form itself—is anybody going to write this down? Alright, because I don't want to waste my breath here, otherwise I will put it in the law. It includes a line that calls for name, strength and then manufacturer, and that information is all in that one line. My recommendation would be that the manufacturer be given a separate space on the form so whenever the healthcare provider completes the MedWatch form, we get the correct name of the manufacturer, because what I am also—and I know you are saying, Steve, that is up to the clinicians—but what is happening out there is that the clinicians are putting the name of the manufacturer, and sometimes it is a generic product and they mistakingly put the name of the original manufacturer. So if we give it a separate line, we are actually saying that we hope the clinician stops and gives it some good thought and actually pulls the manufacturer that is from the drug label itself.

Number 2 is you would also have a separate line that would have the addition of the purchase location of the medication. Now, earlier at one of the other hearings I had said, are we going to have to require doctors to start asking their patients where are they obtaining their drugs, because many of them are either running off to Canada or they run off to an Internet or they go to an Internet site and they are pulling them down from many different sources.

So we have docs out there that are struggling. We have internists and they give their script to their patient, but then we have no idea where the patient then is obtaining the drug and they come back and the doc thinks that the drug which they are prescribing is supposed to get the effect but they are not. He is puzzled. He then switches drugs. So I am trying to figure out how we get to that next follow-on step as we are trying to deal with these counterfeit drugs. These are actions that you can take on your own and I wish you would consider them.

Mr. LUTTER. Thank you very much for sharing them.

Mr. BUYER. Right.

Mr. LUTTER. I made careful note and we will discuss them internally.

Mr. BUYER. All right. Thank you very much. I yield back.

Mr. PALLONE. Thank you. Ms. Schakowsky.

Ms. SCHAKOWSKY. Thank you, Mr. Chairman. Dr. Lutter, I wanted to go back to the subject that Congresswoman Capps raised and that was the New York Times article yesterday. You did not see it?

Mr. LUTTER. I had an opportunity to glance at it only.

Ms. SCHAKOWSKY. OK. Mr. Chairman, I would like to have it included in the record, if I could.

Mr. PALLONE. Without objection, so ordered.

Ms. SCHAKOWSKY. Well, let us talk about the substance of it rather than maybe the specific issue. I will just quote. "The increasing number of FDA drug safety officers who say they have been punished or ignored after uncovering dangerous popular medicines." They talk about this one particular woman and the drug Avandia, but they give a number of other examples. Dr. Andrew Mossholder, in 2003, who discovered antidepressants led some children to become suicidal and the findings—Dr. Mossholder was prevented from speaking to an advisory committee about his analysis. Then Dr. David Ross, in 2006, very concerned about serious illness and death from patients taking the antibiotic Ketek. Is that Ketek? And Dr. Ross met with agency officials and pleaded with them to take action and nothing happened. It ends with a quote from someone still at the FDA, saying that people in this former office of Dr. Johann-Liang were very demoralized. There is a feeling of fear.

Obviously, that is of concern, I think, to us as representing the interests of consumers, if people who do report problems that they have found are being suppressed or even feel the need to leave the agency. This particular issue, this culture that seems to be at the FDA, I think, shows the need for transparency, and there was the inclusion in the Senate version of this bill an action package that would provide the public with documents related to a drug's approval, including a scientific explanation of the risk-to-benefit ratio and a summary review of any disputes and how they were resolved during the approval.

So what I am asking you is, in your experience, is there a culture of, let us say, bullying and intimidation and do you agree that allowing FDA scientists to give voice to their concerns and decisions is an integral piece of the scientific process?

Mr. LUTTER. In my experience, I am unaware of bullying at FDA and I think it would be appalling to me personally and to the FDA leadership, including the leadership of the Center for Drugs and the Center for Biologics and the Center for Medical Devices. We take these concerns expressed in the public very, very seriously.

Ms. SCHAKOWSKY. Well, are you saying, then, that the individuals that are cited in this article are misrepresenting the situation at the agency?

Mr. LUTTER. I am unfamiliar with the specifics of their cases. I do not know the facts about their cases.

Ms. SCHAKOWSKY. Well, what happens when something like this comes to light?

Mr. LUTTER. Let me tell you the commitments that have been made by the FDA leadership to address culture. The Institute of Medicine last fall issued a report that we had asked for, which was openly critical of the agency's ability to address scientific dissent. We responded in a report of our own, the future of drug safety that we issued in late January 2007. At that press conference, Dr. Gaulson and Dr. von Eschenbach made open personal commitments to welcome a diversity of scientific views as well as diversity

of individuals throughout the agency and to a personal responsibility for ensuring that dissent would not be punished.

Ms. SCHAKOWSKY. Well, let me just ask you this. There is a 2006 survey of FDA scientists done by the Union of Concerned Scientists, which found that 40 percent of scientists said they could not publicly express "concerns about public health without fear of retaliation." Are you saying that Dr. von Eschenbach's response is something new that is being done in response to the criticism or that that has always been the policy and that what you are saying is there never was this culture of retaliation?

Mr. LUTTER. I don't know whether there was a culture of retaliation. There is surely a culture of controversy and we acknowledge that, and that has had adverse effects on morale and effectiveness and we are concerned about that. But the key question is, A, we recognize that, and then B, we have laid out, in our response to the IOM report, a whole collection of actions, including personal commitments by the FDA leadership and the leadership of the relevant centers for medical products to ensure that the diversity is not in any way suppressed, is surely not punished, and does not result in any bullying or suppression of scientific views.

Mr. PALLONE. We have to move on. Thank you. Mr. Sullivan.

Mr. SULLIVAN. Thank you, Mr. Chairman. And thank you for being here. A lot of the questions I was going to ask have already been asked and there were other members that were talking about preemption, and you talked about that as well. One thing I would like to talk about is wouldn't you think that conflicting State labeling requirements for drugs, wouldn't that be confusing to consumers and potentially adversely affect public health? For example, if a grandmother was living in Nebraska and visiting her children in Oklahoma and had to get her prescription filled there and had a different notice on the labeling couldn't that be detrimental?

Mr. LUTTER. Conflicting, inconsistent and even contradictory statements about the benefits and the effectiveness and the risk of medical products is surely of concern. How can people figure out what they should be doing if there is not a single voice? The best approach to ensuring safety of medical products is to ensure that there is a single authoritative voice which, through a process of developing the best available scientific information, and evaluating that in a timely and effective manner, can be conveyed to everybody as an authoritative statement, and we believe that is our job. We believe that is our job as a regulatory agency. We have responsibility for regulating the safety and effectiveness of medical products, devices and drugs and biologics. We have been asked to do that by Congress and the American public and we think that if those messages that we convey to the pubic are seen as inconsistent with other authoritative sources, then confusing may result to the detriment of public health.

Mr. SULLIVAN. So you would say that different State labeling would be very confusing and bad to public health?

Mr. LUTTER. If it is seen as inconsistent and incompatible with ours. If we say something and a different statement is made by a State authority, then surely consumers may be confused.

Mr. SULLIVAN. Wouldn't you agree that different labeling would be detrimental to public health?

Mr. LUTTER. Yes.

Mr. SULLIVAN. Thank you.

Mr. PALLONE. Finished? Ms. Solis.

Ms. SOLIS. Thank you, Mr. Chairman. My question is for the director.

Has the FDA ever evaluated whether any of its mechanisms for warning the public, for instance, changes in labeling, are effective in terms of raising awareness for safety issues with products? And are there any plans to evaluate how FDA communicates with the pubic and how effective such measures are and if you have ever looked at that? And then lastly, what kinds of evaluation tools do you have for, say, consumers that don't speak English, whose primary language is something other than English?

Mr. LUTTER. We take very seriously our responsibilities to communicate the information about risks and effectiveness. We recently instituted, in this regard, a new committee on risk communication. Its function is to advise FDA about how to communicate the risks and the benefits of medical products and other FDA-regulated products as well. This committee was first initiated in response to the recommendations of the Institute of Medicine that I alluded to earlier. We anticipate that it will be up and running to have public meetings in the early part of next year. And we are currently soliciting, publicly, nominations from interested experts and people with responsibilities for communication to serve on that advisory committee. One of its functions will be to look at the effectiveness of our efforts generally. This is, we think, an area that is important and could be greatly strengthened by work of this committee.

Ms. SOLIS. And what about reaching out to groups that its primary language is not English? How do you communicate with them?

Mr. LUTTER. We do have a plain English program at FDA. We have a variety of outreach efforts that run through the Office of External Relations to representatives of minority groups and people for whom English is not the primary language.

Ms. SOLIS. Has that been evaluated?

Mr. LUTTER. The effectiveness of that has not been separately independently evaluated.

Ms. SOLIS. That probably should be looked at, because of course there are degrees of education with different groups from different backgrounds and I would even say English, in terms of just the type of individuals that may have no more than an eighth grade education and may not—labeling obviously has to be simplified in some format; but to find also different groups, Asian as well as Hispanic, that may not be fluent in English to have appropriate culturally competently appropriate language that is made available to them, because that could even be misconstrued and obviously lead to abuses.

Mr. LUTTER. We would be very happy to take that suggestion into advisement as a topic for the advisory committee when it has its first meetings next year.

Mr. SOLIS. And I would hope, just as a follow-up, too, I know that sometimes we often talk about the Internet and put posting information to the public. But by and large, the Hispanic community

and African-American community and in rural areas are not privy to access to the Internet. So I would encourage more outreach either through form of radio, newspapers and things of that nature that can actually be a lot more helpful in terms of providing better consumer information, and obviously testing focus groups, I think, could be helpful as well. And that is a comment.

Lastly, I wanted to ask you, what has the FDA done to decipitate what I see as tensions between some of the staff that you have doing oversight, monitoring, those that are evaluating and those that are actually helping to approve some of the drugs and devices that are coming forward? I understand that there has been occasion where morale has not been one of the highlights of the agency.

Mr. LUTTER. Before turning to that, thank you, let me first add a comment that I should have made earlier about the evaluation of risk communication. There is a reevaluation of risk management tools, broadly, as part of our PDUFA IV reauthorization. We look forward to using PDUFA IV resources to do that reevaluation.

With respect to the culture issue, we recognize this is important. There is a variety of essentially management efforts in the individual centers to identify, if you will, best management practices and communicating, communications between supervisors and staff and surely to support diversity, not only of people according to their demographic backgrounds, but also of scientific views and scientific thought. We have a very diverse agency with respect to the multiplicity of scientific backgrounds and expertise that is represented. Many people bring different views and perspectives to the table because of their training. The determination of safety and efficacy for drugs is something that requires many, many different types of experts, not just MDs.

Ms. SOLIS. What kind of concrete things will you be instituting, because my understanding, if I could just reiterate, the tension is between the pre-approval review staff and the post-marketing safety staff.

Mr. LUTTER. There are ongoing regular workshops and new meetings internal to CDER, to ensure that communication and respect among those different staffs is enhanced as much as possible.

Mr. PALLONE. We have to move on.

Ms. SOLIS. Thank you, Mr. Chairman.

Mr. PALLONE. Thanks. Mrs. Blackburn.

Mrs. BLACKBURN. Thank you, Mr. Chairman. Thank you for your patience. I want to be certain that I am understanding your remarks, since we didn't have your testimony in advance and it seems you have five major problems with the legislation. And just to recap with you, one would be that it is too focused on process and structural changes; No. 2 would be the breadth of proposed requirements for risk evaluation; No. 3 would be the existing FDC Act labeling requirements dealing with the med guides, et cetera; No. 4 would be the risk map provisions; and then fifth would be the DSOB oversight and review for disputes. So it seems as if that pretty much encapsulates the problems that you have with the legislation.

Then you go on, on page 14, and you talk about a better overall strategy is to be sure you have appropriate resources. And Dr. Lutter, I would just like to highlight with you, going back to some

of our other hearings that we have done, sometimes the public has a real problem with giving more resources to an agency that seems to have difficulty in fulfilling their mission or understanding their mission, maybe, and there seems to be a frustration when there is a lack of best practices in place with a certain agency and when there seems to be a communications problem between different divisions not knowing what another division is doing, and then maybe even one division telling another one don't take action there, we don't want you to do that, when a person feels as if they are doing their job.

So I would highlight with you that those are concerns. We still are looking for that list of best practices. We still want to be certain that you all are putting the needed transparency in place when you are dealing with adverse reactions. And going through the process of quantifying these, you mention at the bottom of page 14 your analytical tools and approaches that you use with turning that raw data into appropriate questions and practical information. Some transparency through that process would be very helpful, I think, not only for you all, but for us.

I have got a couple of specific questions before my time runs out. The REMS process. In the discussion draft, the way the changes are written there, would all safety labeling on drugs have to be approved by the FDA, if you were to take the action from the discussion draft?

Mr. LUTTER. Yes, that is our understanding.

Mrs. BLACKBURN. It would all have to be approved by the FDA. OK. And then another place in the discussion draft they talk about a non-promotional summary of the results, as they are talking about the clinical trial registry and the results database. I don't see non-promotional summary defined anywhere. So do you all have a definition of that? And then the flipside of that question would be, is writing a factual summary then considered to be a promotional? If something has favorable results and you are writing, would that be considered to be a promotional summary? And if you need to come to that one in writing to us later, that is fine, but insight on that would be helpful.

Mr. LUTTER. If I could try and take it orally here, I will do what I can do. One thing I have not had an opportunity to talk about because part of the complexity of the legislation is the clinical trials registry and particularly the requirement for this results database that I think you are referring to. And a key question is what we would mean by an appropriate summary of the results, and the difficulty with that is that the studies are essentially designed to answer specific questions. But later on, when they find that the results of the study designed to answer question A may be very, very interesting or helpful with respect to other questions, and in that sense this non-promotional summary is something that may be actually quite problematic to implement from an operational perspective. So we have——

Mrs. BLACKBURN. So the non-promotional would be problematic?

Mr. LUTTER. Yes, but we have concerns generally about this results database and the key question is what would constitute an appropriate summary of results in this results database. We think

that may be a very difficult requirement actually to implement in practice.

Mrs. BLACKBURN. And do you have any guidance going on forward on that as you look at the legislation to make it workable and practicable?

Mr. LUTTER. Our understanding is that there is currently a pilot project underway, in cooperation with NIH, to look at how one might summarize this information in an effective way and we think that might provide a way to identify, first in practice using this pilot project, appropriate information before implementing on a much broader scale.

Mrs. BLACKBURN. Well, with the pilot project at NIH, I would just highlight with you, one of our concerns many times is the lack of communication that seems to exist between the FDA and NIH, and probably a bit more transparency there would be helpful as you would look at how NIH would go about trying to figure this out and make it workable. I have got two more questions. What I will do is submit those and then yield back my time so that everyone gets their questions in before votes. Thank you.

Mr. PALLONE. Are you completed? OK. Thanks. Mr. Green.

Mr. GREEN. Thank you, Mr. Chairman. During the negotiations on the medical device fee, Dr. Lutter, the FDA and the device industry agreed on changes to the Third-Party Inspection Program that were not adopted in the discussion draft that is before today. If the program were utilized to increase the rate of inspections, I would like to see us enact improvements in the program. However, concerns remain about the potential for conflict of interest increasing with increased reliance on these third-party inspections. If we were to adopt the changes you negotiated, what safeguards are included in your proposal to address these conflicts of interest? And would that proposal limit in any way the FDA's ability to directly inspect a facility? And the next to the final one was, how much money would the FDA need to conduct its own inspections? Is it a question of resources?

Mr. LUTTER. Let me try to answer them in reverse order. I don't know the answer to how much money it would take. It is a question of resources, but more than just in the sense that we could do more with more. It is really a question of is it wise to be doing it and using our resources in this way, when we think that there is higher risk that could be better addressed with use of the same resources? In that sense it is really an efficiency concern rather than the concern with the amount of resources overall. I am sorry.

Mr. GREEN. On the issue of if we use outside or third-party inspection programs, I am concerned about the third-party conflict of interest. Obviously, we have the problem within the FDA, but would we see it even worse with third-party inspections?

Mr. LUTTER. We believe that it would surely not be worse with respect to third-party inspections. We would reserve the right to be able to inspect any facility on our own and we would be verifying that the skills, the appropriateness of the third-party inspectors, before they go out to do their third-party inspections. So in essence, you can see it in a way as double protection. We are certifying the inspectors and then we reserve the right to do inspections on our own.

Mr. GREEN. OK. Another question. The discussion draft—language that would require the GAO to study the 510(k) process for the approval of medical devices. We know that a large majority of devices are approved using the 510(k) process. However, one of our witnesses on the second panel suggests that we prohibit the use of the 510(k) process for implantable devices and mandate that each implantable device go through the PMA process. Your understanding is that the 510(k) process is utilized primarily for class I and class II devices. Can you quantify for us how many class III implantable devices utilize the 510(k) process for approval?

Mr. LUTTER. I will have to get back to you on that. I don't know.

Mr. GREEN. OK, I appreciate it. And that last question. I continue to be concerned about structural issues at FDA that weigh the agency too heavily towards drug approval. While your statement suggests that the drug safety draft focuses unnecessarily on structural changes, it doesn't contain some of the structural changes such as a separate, independent Office of Drug Safety that some on our committee have advocated for. Under the REMS framework, would you support language giving the Office of Drug Safety the ability to request a REMS change such as an additional post-market study to help level the bureaucratic playing field for the Office of New Drugs?

Mr. LUTTER. Well, we think that a lot of the conversations within CDER about risk, require also a consideration of benefits, because the real question is, in addressing drug safety questions, is that the safety issue is very difficult to evaluate on its own, independently, without asking or evaluating how effective is this drug at providing the benefits to the patients who need it. And in that sense, we think that the best way to proceed is with improved communications that we are working on with the consideration by the relevant parties within the Center for Drugs and that is what we are planning on doing.

Mr. GREEN. OK. Would you support language giving the Office of Drug Safety the ability to request an REMS change such as an additional post-market study? Could we give that authority to the Office of Drug Safety?

Mr. LUTTER. We would prefer that that authority not be prescribed through statute. That is a particular change within a small office within FDA. We think that the responsibility should reside with the management of the Center for Drugs and with the Commissioner.

Mr. GREEN. OK. Thank you.

Mr. PALLONE. Thank you. Mr. Murphy.

Mr. MURPHY. Thank you, Mr. Chairman. Welcome here. A couple questions regarding the issue of allowing exclusivity for a limited number of months after some new treatments have been found. In particular, I am concerned about pediatric drugs for orphan diseases. As you know, there is a separate act that controls some of the aspects of dealing with orphan drugs, whereby the timeframe may be—we provide Federal grants and contracts for clinical trials. There is tax credits, up to 50 percent for clinical testing costs and exclusive marketing rights for 7 years. This, of course, is important because some of the orphan drugs have such a small number of children or patients that they may influence. I am concerned that

if we are too broad in our approach of saying that there is 3 or 4 or 5 or 6 months exclusivity, that is hardly enough time to recover the cost of research for some of these things and we know that the expenses, however, can be extremely high because there are so few people that take these medications, in some cases, where the costs of development, even if it is an adaptation of an adult to pediatric drug.

What I would like to know is, should Congress act in legislation, such as PDUFA or others, to make sure we protect the exclusivity rights of orphan drugs in these cases, so that companies are more willing to make some investments into research on those drugs?

Mr. LUTTER. Could I ask for clarification?

Mr. MURPHY. Yes.

Mr. LUTTER. The question is, so you are not asking about the exclusivity period for BPCA and with respect to pediatrics?

Mr. MURPHY. Yes. I want to make sure that we are not stepping on the toes of the orphan drugs, so that we still are providing enough incentives for companies to research treatments for some of these diseases where there is a smaller number.

Mr. LUTTER. Our understanding is that, currently, the sponsors can get exclusivity of 6 months under BPCA and they also have orphan exclusivity under 7 years, and that provides incentives that are fairly robust with respect to the need to protect children.

Mr. MURPHY. I just want to make sure, in your review, as we look at this legislation, if you could review it carefully in making sure that we maintain those issues there.

It is very important. Let me go to a second area here and that has to do with us looking at some of the adequacies of medication to see if this is the right bill to do that. I am concerned about antibiotic-resistant strains for infections that are forming. And I am concerned that there a number of strains have developed, which one medication is no longer able to treat them. And if there are some things that we should be doing with this, also, that as drugs are reviewed in terms of their effectiveness, we are not only looking at side effects in terms of harmful things that may come as side effects of taking medication, but also reviewing side effects that may come from overuse or inappropriate hospital or healthcare practices that may also contribute to the spread of infections that whereby we are creating drug-resistant strains. And I don't expect you to answer this now, but it is one that I consider pretty important, because so often we name a specific drug and we say it has this association with heart problems or diabetes problems, et cetera.

But there are also practices, I think, in the practice of medicine, that contribute to problems, iatrogenic effects and nosocomial infections that occur, which in turn can make some medications useless. So I am hoping that one of the things you could look at with us, also, is provide suggestions of how when reports are made on medications, that we are looking to see if it is the practice that is also leading to some problems with that as well, not just the medication itself.

And a third point has to do with something that is more of using medical devices. Now, with the medical devices, as you know, some of these are being reused, sterilized and reused, and that may work

in some cases, in other ones I have some concerns. For example, do you think that patients have the right to know and to choose when a medical device designed for single use has already been used on another patient before it is used on them?

Mr. LUTTER. Our broad concern is that the labeling should be related to risks. And if the reuse or the manipulation of the product to ensure reuse is one that is well enough managed that there is no appreciable risks or concern to the patient, then the need for labeling is not clear.

Mr. MURPHY. Well, that is something, I guess, when one says appreciable risks, does that include giving at least that information to the patient, that we have determined that there is no appreciable risk from reusing this equipment?

Mr. LUTTER. It is also a question that a patient could ask a doctor about whether or not the particular——

Mr. MURPHY. What if a patient doesn't know to ask?

Mr. LUTTER. Well, then there is a variety of opportunities for doctors to provide information to patients that may be of interest to the patients.

Mr. MURPHY. Well, this is another one those areas, Mr. Chairman, where I hope we can get some more clarification to make sure that in these cases where there may be some increased risk for infection control, to find ways we can adequately address that and I appreciate that. Thank you, Mr. Chairman, and thank you.

Mr. PALLONE. Thank you. Mrs. Myrick.

Mrs. MYRICK. Thank you. Thank you for being here. I had a question relative to the medical devices and the approval procedures. The 510(k) process, I understand, basically has been in use for a long, long time and that 98 percent of the devices are approved under that procedure. But basically, if a device is just an improvement over something that maybe failed or whatnot, it is OKed or allowed to be on the market? My question is because I had myself a jaw joint replacement, which is not real common, and there was very little information available about what was available to me to use, because it is not an area where there has been a lot of research, et cetera. And I am trying to find out on everything, you all had on your Web site and every place else I could go to see just what was being done.

My question is: where do you get your feedback for knowing whether something is really working or not? And does this come from doctors, because this particular surgery is fairly rare and a very small percentage of doctors who do it correctly, so there is not a lot of background testing. It hasn't been done for that long. And I am just curious as to how this process really works, because what do you know ahead of time and how, in this particular case, I guess I am referring to, how much background information is available before you approve something. And then what kind of feedback do you get as you are going through the process?

Mr. LUTTER. Well, with respect to 510(k), the key issue is one of equivalence. Is it really similar to something that is already on the market?

Mrs. MYRICK. Right.

Mr. LUTTER. And I think, with respect to the information that we receive, it is useful to draw a distinction between the risk of use

of the product and other measures of effectiveness or just outcomes very broadly. And in particular, one can imagine it with an implantable device. What matters is also the quality of the surgery as well as simply the device and then there may be measures of the effectiveness of the device that vary over time, if it is implantable, that are also harder to measure. We do track the adverse events. We get information from the manufacturers on that. They are obliged to give us information about——

Mrs. MYRICK. So they are required to do that?

Mr. LUTTER. Yes, to pass on to us information that they have from any source, about the adverse events associated with products that they produce. So in that sense, yes, we do have that information. But I think that, from a patient perspective, it is probably useful to know that there is a collection of information about just the—think of it as the effectiveness or the success, if you will, of the surgery. That is not necessarily in FDA jurisdiction, because it is not really the product that we are regulating. It is the service that is associated with that product.

Mrs. MYRICK. Yes. And there are a lot of surgeons who are not being effective in the way they do it, I know that. You feel that the process, the way you are doing it currently, is an acceptable, effective process?

Mr. LUTTER. We collect information and we collect information from the manufacturers, who are obliged to pass on all of the information that they have to us about the adverse events. And in that sense, we have information about the adverse events associated with the product that we regulate. That part of it is satisfactory. I think a real question is where one would wish to go in the future if one were designing a better program and we have a couple of ideas in that regard that I talk about here.

Mrs. MYRICK. That was going to be my next question.

Mr. LUTTER. One is with respect to unique device identifiers, where we might be able to better notify patients in the event that there is some evidence of unexpected adverse events or harm or recall or something like that, more broadly outside the area of devices, but also with respect to drugs. I talked earlier today about a public/private partnership with vigilance. That is something that is mentioned, at least, in the Senate draft and in the discussion draft here. We think that tying that with respect to the Reagan-Udall Foundation would be an effective way to manage it. That sort of partnership offers several great strengths. One is probably a perception of neutrality and respect. It would be FDA along with many other partners. And it, in principle, would allow for a very timely expedited access to this sort of information through interlinked databases that would permit and facilitate faster identification of safety signals that would let us develop the subsequent studies in a timely way, as to better inform patients and their doctors.

Mrs. MYRICK. But if all of that is implemented, et cetera, what kind of timeline are you looking at for implementing the process?

Mr. LUTTER. Well, it is difficult to say. This sort of thing has not been done previously, so it is really difficult to say we could do it within *X* months. But in terms of a vision of what the future might look like in a world where only 5 years ago, people weren't walking around with BlackBerries and cell phones as they are today. So

what would one envision the world of the future to look like, and that is the vision that we have.

Mrs. MYRICK. Thank you. My time is up.

Mr. PALLONE. Thank you. Mr. Hall.

Mr. HALL. Mr. Chairman, thank you. We have been in and out here. Each of us have two or three committee hearings going on right now and if I ask a question that has already been asked and you have fear that you won't answer it the same way you did earlier, why I won't press it. But Mrs. Blackburn asked you and set out to you, I think, five of your concerns here. I didn't hear any concern about any constitutionality of that, Dr. Lutter, that you are dealing with. The draft bill contains a provision that would require the pre-clearance of DTC ads and places a moratorium on these ads for new products. Does that give you any constitutional concern?

Mr. LUTTER. Thank you for asking the question. It is not something I have had a chance to talk about earlier today. FDA has a repository of expertise in drugs, devices and food and their safety and efficacy and not in constitutional law. We are told, however, that this raises concerns from a constitutional perspective and we caution about progress in implementing a provision that may, because of constitutionality questions, be difficult to implement and enforce in an effective and timely way.

Mr. HALL. Well, the reason I asked this is for a different reason than that and I didn't make a very good grade on constitutional law when I was at SMU. And I want to know the nature of these provisions that seem like they could expose the agency to some lawsuits, and I think that you all would have had some discussion on that.

Mr. LUTTER. We are concerned about litigation risk, generally, litigation ties up agency resources in a really dramatic way and it provides uncertainty about how we can implement our programs. And a real question, ensuring that the programs are implemented in an effective and timely way, would involve consideration of litigation risks and yes, we have had these conversations. But the advice on constitutional law is probably one that would best be given by parties other than FDA.

Mr. HALL. Are you an attorney?

Mr. LUTTER. No, I am not, sir.

Mr. HALL. The ladies behind you that are advising you, have they been into this?

Mr. LUTTER. Some of them have talked about this, but I think what you will hear is that there are experts in constitutional law that are best equipped to address this from outside of FDA.

Mr. HALL. Given the Western States case, do you think that preclearance might withstand judicial scrutiny? Do you have an opinion on that? Come on, give me an answer.

Mr. LUTTER. I am not equipped to answer that. I don't have——

Mr. HALL. Well, if I answer it for you, then if so, would this requirement take away resources from other drug safety activities? It would, wouldn't it?

Mr. LUTTER. Tying FDA up in litigation will take resources away from our other activities.

Mr. HALL. Let me shift my gear here just a little bit. Would a mandatory REMS system improve drug safety, or could a mandatory REMS, for every drug, actually divert FDA resources?

Mr. LUTTER. Well, the mandatory REMS for all, if applied to all drugs, is going to divert it, because we think there is a class of drugs where that sort of attention is not needed. The best procedure that we have as an analog to the REMS is the RiskMAPs, which currently applies to a fraction of the products that we approve.

Mr. HALL. It makes sense. Under one of the drafts, to shift again—well, not really a total shift, but on one of the drafts, a company could face a fine of up to 10 percent of U.S. sales for violating a REMS. One component of a REMS is for the manufacturers to ensure that a physician or a pharmacy is not violating the REMS and if they are to restrict access to the product to that entity. So my question then would be, does a manufacturer have direct control of the products it moves to the pharmacies? Does the manufacturer have a direct control of the products it moves to the pharmacies? Or do manufacturers most often sell to wholesalers?

Mr. LUTTER. They most often sell wholesale, so any control is at best indirect.

Mr. HALL. Then, I guess my follow-up question and my final question, is it fair for a company to be subject to such a fine for which they have no direct control?

Mr. LUTTER. Well, only to the extent that they have control, would it be fair?

Mr. HALL. If they had no direct control.

Mr. LUTTER. I guess, if they have no direct control, there is a real question about the appropriateness of the fine.

Mr. HALL. Well, that is a pretty good answer and I thank you and I yield back my time.

Mr. PALLONE. Thank you. I think you have stayed here long enough to clear the podium and we appreciate it. Or clear the dais, I should say. But I appreciate your bearing with us. It has been pretty difficult, I think, to answer all of these questions and you have done so, for the most part. So thank you for being with us. I know a lot of Members asked you questions for which you said you would get back to us in writing, so please do so as quickly as you can and we appreciate you being here today.

Mr. LUTTER. Thank you for the questions and diversity of views and we look forward to working with you on implementing and passing this legislation in a timely way.

Mr. PALLONE. And we hope to do so in an expeditious way and I know that makes it difficult sometimes, but I agree that we have no choice, given the time constraints. Thanks again.

Can I ask the second panel to come forward? I guess I should mention, while you are getting seated, that we do expect some votes that might interrupt the second panel or the questions, but right now the House is in recess, so we are going to proceed until there is a vote. So we may just get right through it. I don't know.

OK, if everyone is seated, I want to welcome our second panel and let me mention who is here. I will go from my left to right.

First, on our left is Dr. Caroline Loew, who is the senior vice president for science and regulatory affairs for PhRMA. And then

we have Mr. James Guest, who is president and CEO of the Consumers Union. Then we have Mr. Steven Ubl, president and CEO of Advanced Medical Technology Association. And then we have Dr. Diana Zuckerman, who is president of the National Research Center for Women and Families. And then we have Mr. Steve Walker, who is co-founder and chief advisor for Abigail Alliance for Better Access to Developmental Drugs. And last is Dr. Richard L. Gorman, who is chair of the AAP Section on Clinical Pharmacology and Therapeutics for the American Academy of Pediatrics.

Let me again say that you may get some questions from the subcommittee members that you would have to answer and follow up in writing. With the discretion of the chair, we will certainly do that. And we will start for 5 minutes with Dr. Loew.

STATEMENT OF CAROLINE LOEW, SENIOR VICE PRESIDENT, SCIENCE AND REGULATORY AFFAIRS, PhRMA

Ms. LOEW. Mr. Chairman, Ranking Member Deal and members of the subcommittee, I want to than you for inviting me back to testify today about our shared commitment to strengthen the safety of America's drug supply. My name is Dr. Caroline Loew and I am the senior vice president for scientific and regulatory affairs for the Pharmaceutical Research and Manufacturers of America, or PhRMA.

I return today to this subcommittee to reiterate the commitment on the part of PhRMA, and its member companies, to work with the FDA and other stakeholders to improve our drug safety system in a way that preserves innovation and patient access. No other issue carries more importance to our industry than patient safety.

PhRMA believes that the FDA's proposal to reauthorize the Prescription Drug User Fee Act, or PDUFA, will provide the agency with the tools and resources necessary to make a good system even better, ensuring that FDA's drug review and monitoring systems keep pace with 21st century science.

Since 1992, PDUFA has been a crucial program for FDA and the pharmaceutical industry, but most importantly for patients. The increased funding provided through user fees has enabled the agency to review new drug applications in a thorough and timely manner, without compromising its exacting standards for evaluating safety and efficacy.

The reauthorization proposal under consideration that has been forwarded by the FDA includes new resources that would enhance and modernize FDA's Drug Safety Program, specifically providing nearly $150 million over the next 5 years, including 82 additional staff for post-market safety activities. These additional resources would also allow the agency to increase its use of modernized techniques and tools for the assessment of drug risks. PhRMA also supports the inclusion of funding to advance FDA's Critical Path Initiative, as well as legislation establishing the Reagan-Udall Institute to conduct related research.

Just as drug safety fundamentally involves a balance between benefit and risk, so should the process of reforming an already successful and effective system.

The proposed Risk Evaluation and Mitigation Strategy, or REMS process, creates a complicated and bureaucratic safety oversight

system that may not be workable in practice, and which if applied to all drugs would be overly burdensome for the FDA. At the very least, use of REMS should be limited to and focused on higher risk products that warrant more rigorous post-marketing monitoring.

The anti-preemption language in the REMS and other discussion drafts is also a significant concern. This provision would undermine the intent of the REMS bill to reinforce FDA's control over drug warnings, because it would enable each State to require warnings the FDA specifically rejected based on its scientific review. Such conflicting warnings could cause considerable confusion for patients and their physicians.

Further, the civil money penalties for REMS violations that will be allowed under the discussion draft are unreasonable. Punitive fines as high as 10 percent of U.S. sales are excessive and may be a particular issue for small to midsized companies.

Limitations on direct-to-consumer, or DTC, advertising imposed under the discussion draft would not be in the best interest of patients. Restrictions on advertisements would deny patient access to important information, which repeated studies have shown to be valuable in educating patients and fostering patient/physician dialogue.

Additionally, FDA's PDUFA proposal already provides the agency with enhanced resources to pre-review DTC advertising through a new dedicated user fee, further helping to ensure that benefits and risks are clearly and accurately communicated in DTC advertisements.

Instead of the broad reforms proposed, PhRMA would favor targeted drug safety enhancements to address key issues. For example, we support the creation of a robust post-marketing labeling program that would give FDA greater authority to require a labeling change and to complete the process in an expedited manner when warranted.

The current Pediatric Exclusivity Incentive Program has been a tremendous success and PhRMA supports continuing it as currently authorized.

According to the FDA, the Best Pharmaceuticals for Children Act, or BPCA, has done more to spur research and generate information about the use of medicines in pediatric patients than any other Government program. Changes in the current program, particularly the proposed exclusivity adjustment, or tiering of exclusivity, could reduce the incentive to conduct pediatric studies.

Ultimately, it is important to recognize that FDA's current drug safety system is robust and effective; however, there is always room for improvement. FDA needs more resources to enhance and modernize its already strong drug safety monitoring system, and the PDUFA IV proposal submitted by the FDA achieves this. As such, we urge Congress to quickly reauthorize it.

Thank you for this opportunity to inform the subcommittee about PhRMA's perspectives in this critical public health arena. Thank you.

[The prepared statement of Ms. Loew follows:]

TESTIMONY OF CAROLINE LOEW, Ph.D.

SENIOR VICE PRESIDENT

SCIENTIFIC AND REGULATORY AFFAIRS

PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA

BEFORE THE SUBCOMMITTEE ON HEALTH

COMMITTEE ON ENERGY AND COMMERCE

UNITED STATES HOUSE OF REPRESENTATIVES

LEGISLATIVE HEARING ON DISCUSSION DRAFTS CONCERNING PRESCRIPTION DRUG USER FEE ACT REAUTHORIZATION, MEDICAL DEVICE USER FEE AND MODERNIZATION ACT REAUTHORIZATION, DRUG SAFETY, AND CERTAIN PEDIATRIC PHARMACEUTICAL AND DEVICE LEGISLATION

June 12, 2007

A. Introduction

Mr. Chairman and members of the Subcommittee, thank you for the opportunity to testify today on the discussion drafts intended to reauthorize the Prescription Drug User Fee Act (PDUFA), further ensure the safety of the nation's drug supply, and reauthorize important provisions facilitating pediatric research, i.e., the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA).

My name is Caroline Loew, Ph.D., and I am Senior Vice President of Scientific and Regulatory Affairs at the Pharmaceutical Research and Manufacturers of America, also known as PhRMA. PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, healthier and more productive lives. Our member companies invested more than $43 billion last year in discovering and developing new medicines for American patients. It is thus no overstatement to say that PhRMA companies are leading the way in the search for cures.

PhRMA and its member companies consider reauthorization of PDUFA, drug safety, and reauthorization of BPCA and PREA to be top priorities. PhRMA appreciates the opportunity to provide our views to this Subcommittee on these critical issues.

B. Reauthorization of PDUFA

Reauthorization of PDUFA is one of the more important legislative issues facing Congress this year. Since its enactment in 1992, PDUFA has brought about tangible benefits to patients, the FDA, and the pharmaceutical industry. FDA's appropriated resources have been augmented by industry user fees, providing the Agency with

sufficient resources to conduct reviews of new pharmaceuticals in a thorough and timely manner assuring widespread patient access.

Since its original passage in 1992, PDUFA has been a crucial program not only for FDA and the pharmaceutical industry, but also – and most importantly – for patients. By leveraging industry user fees, FDA has been able to review and act on new drug applications (NDA) and Biologic License Application (BLAs) in a timely manner. Life-saving medications are routinely available to patients within six months of submission of the NDA, an important public health achievement. Widespread access to new cancer and HIV medicines has markedly improved the outlooks for patients suffering from these diseases.

Throughout the PDUFA programs of the past 15 years, the exacting standards by which FDA evaluates NDAs and BLAs have not been altered. What has been altered is the level of resources available for FDA to perform its critical function of reviewing safety and effectiveness of potentially life-saving medications. Funds go to FDA's general drug and biologic budget and simply are used to hire additional staff to allow FDA to perform its critical drug review functions while maintaining the same exacting standards for safety and efficacy (demonstrated by the fact that the drug withdrawal rate pre- and post-PDUFA has remained constant at just over 3%).

The FDA's PDUFA-IV proposal is no exception to this approach, and contains important new provisions and resources to:

- enhance and modernize the FDA drug safety program,
- add a new user fee program to give FDA additional resources to review and provide advisory opinions on direct to consumer television advertisements,

- improve drug development, and
- provide more stable financing for the program.

Although the industry-funded part of the drug review process will increase during the PDUFA-IV years, patients will be well served by a more predictable drug review process and assurance that the robust drug safety office within the Agency will be enhanced and modernized.

The substantial new funding provided to enhance and modernize the FDA drug safety system – nearly $150 million dollars over the next five years – will continue to assure that FDA's pre- and post-market safety assessment system is the world's best. These funds substantially address the relevant recommendations on FDA resources and the science of safety that the Institute of Medicine (IOM) issued last fall in their report on the US drug safety system.

These additional resources will be used to reduce FDA's reliance on the spontaneous reporting of adverse events and increase use of modernized techniques and resources, such as epidemiology studies and large medical databases, to identify risks more quickly and accurately. FDA needs to be able to use new IT systems, access to electronic health records, new algorithms for detecting drug safety signals, as well as new approaches to validating drug safety signals. Funding is provided in the PDUFA-IV proposal to move towards this future.

The PDUFA-IV proposal also includes a new user fee for direct-to-consumer ("DTC") television advertisements. This will allow FDA to hire 27 additional employees to review drug advertisements *prior* to public dissemination, helping to ensure that benefits and risks are clearly and accurately communicated. It also will create strong

incentives for companies to submit television advertisements to FDA before airing them, thereby directly supporting full implementation of the PhRMA *Guiding Principles on Direct-to-Consumer Advertising About Prescription Medicines* ("*Guiding Principles*"), which have been extremely effective over the past year and a half at improving the level of DTC communications.

This PDUFA proposal also continues forward with suggested improvements to the drug review process. FDA will implement the good review management principles that were formulated during PDUFA-III. FDA will communicate to sponsors a timeline for discussing labeling and post-market commitments in advance of the action date. This will improve the predictability of the drug review process and lead to more meaningful post-market studies that are appropriate for the new drug.

Funding is allocated for the purpose of increasing the efficiency and accuracy of drug development. This will permit FDA staff to be directly involved in external activities such as partnerships and consortia that are generating data and information that will create new paradigms for drug development. In return, FDA commits to developing draft guidance in areas related to safety assessment, clinical trial design, and the use of biomarkers. In addition, FDA will participate in workshops and other public meetings to explore new approaches to a structured model for benefit/risk assessment. The results of these interactions will be used to assess whether pilot(s) of such new approaches can be conducted during PDUFA-IV. Collectively, this will lead to new paradigms leading to more efficient and accurate drug development resulting in earlier patient access of important therapies.

C. Drug Safety

When considering potential drug safety legislation, PhRMA believes that Congress should keep in mind the following principles:

- The current drug safety system is robust and effective but could be made even better with additional resources and better use of modern scientific techniques and resources for identifying and assessing risks.
- Assessment of safety concerns must always be undertaken with full knowledge of the benefits (efficacy) of a drug. Drug safety is a balance between benefit and risk. This is critical as any assessment that focuses solely on risk will lead to decisions that will have an adverse impact on the public health and patients.
- Drug safety is an ongoing process that begins long before a medicine enters the marketplace and continues long after it has been made available to patients. Drug safety does not stop at approval.
- Any drug safety reforms should strengthen FDA's oversight capabilities without impeding innovation or interfering with patient access to needed medications. This is particularly important for patients with serious or life-threatening diseases and patients living in rural areas.

1. The Current Drug Safety System Is Robust

Despite recent concerns expressed about FDA's ability to ensure drug safety, it is important to recognize that FDA's current drug safety system is robust and effective. From the approval process through post-market surveillance, the system is working well. This is reflected in the fact that over the last 20 years, about 97 percent of prescription

medicines approved for patient use in the U.S. have safely remained on the market, while only about 3 percent of medicines have been withdrawn for safety reasons.

Before a drug is ever allowed on the market, it must undergo a rigorous pre-market testing and approval process that often spans between 10 to 15 years. Drug safety testing starts early in the development process through a series of laboratory tests, animal tests, and then with very small numbers of volunteer patients, and continues through large scale Phase 3 clinical trials involving on average several thousand patients. Because the science is constantly evolving, pre-approval safety testing is much more rigorous today than it was even ten or fifteen years ago. Companies now routinely test for safety issues that once were poorly understood, could not be predicted well, and for which there were no accurate tests. For instance, today a company will often assess whether a drug causes QTc interval prolongation, a rare but serious side effect which could cause heart arrhythmia, and similarly will often assess the liver toxicity of a drug, which is again a rare but serious side effect associated with some drugs. As a result, we typically know far more about the safety profile of a drug that is approved under today's standards and science than ever before.

The FDA's post-market surveillance system also is robust and constantly improving. Once a drug is approved, safety is monitored continuously as long as it is on the market through a collaborative process involving FDA, pharmaceutical companies, healthcare providers and patients. Physicians, nurses, and other healthcare providers are on the front-line of drug safety; they are often the first to learn of a potential problem with a medicine and are encouraged to report issues or concerns promptly to the FDA or the company concerned. Companies likewise play a critical role in assessing new and

emerging risks with marketed medications, with dedicated teams of experienced physicians and scientists whose job is to collect and analyze safety data on a daily basis, and to immediately report any potential problems to government authorities.

2. PhRMA Supports the Safety Improvements In PDUFA and Carefully Targeted Revisions to FDA's Authority

Although the current drug safety system is robust, even a good system can be made better. PhRMA believes that FDA's drug safety system could be significantly improved with additional resources and a more modernized approach. FDA's most urgent need is not additional authority; rather, FDA needs additional resources devoted to drug safety activities and an approach that takes full advantage of the latest scientific tools and resources.

The FDA's proposal to reauthorize PDUFA, as discussed above, includes significant new funds for FDA to enhance and modernize the drug safety system. The PDUFA-IV proposal provides approximately $150 million over five years to allow FDA to (1) hire 82 additional staff for drug safety activities, including experts in epidemiology; (2) increase use of modernized techniques, such as epidemiology studies and large medical databases, which contain a wealth of drug safety information; and (3) reduce FDA's reliance on spontaneous adverse event reports. The PDUFA-IV proposal also removes the three-year time limitation so that FDA can use funds from the user fee program to address safety issues whenever they emerge.

PhRMA believes that the robust drug safety provisions in the PDUFA-IV proposal address FDA's drug safety needs. These new provisions, along with FDA's own internal reforms, should be allowed to work to enhance and modernize the drug safety system. We are concerned that adding significant new authorities and a markedly

different review paradigm, such as the Risk Evaluation and Mitigation Strategy (REMS) proposed in the discussion draft, may actually be counter-productive. The REMS process creates a complicated and bureaucratic safety oversight system that may not be workable in practice. These additional processes may end up impairing drug safety oversight by miring FDA safety officers in unproductive bureaucratic exercises rather than meaningful safety surveillance activities. They also will add significant costs to the drug development process, thereby impairing innovation and impeding access to life-saving medications. This is particularly the case as the REMS process envisioned in the House discussion draft will be applied to all drugs, rather than targeted at those showing safety signals that warrant more rigorous post-market safety monitoring. At the very least, targeting use of the REMS, and hence limited FDA resources, on higher risk products would be a more appropriate approach.

If Congress believes that the drug safety enhancements in the PDUFA-IV proposal are not sufficient and that FDA needs additional authorities, this should be accomplished through carefully targeted revisions to the Federal Food, Drug, and Cosmetic Act ("FFDCA" or "the Act"). While PhRMA believes that FDA's existing authorities are sufficient to ensure compliance with all applicable regulatory requirements, PhRMA nevertheless would support targeted revisions to the Act to clarify FDA's authority provided such revisions do not impede innovation or interfere with patient access to needed medications. Significantly, the targeted revisions discussed below can be accomplished *without* creating an entirely new bureaucratic maze. In particular, PhRMA would support the following revisions:

Clinical Trial Registries and Databases. PhRMA and its member companies are committed to the transparency of clinical trial information. Consequently, PhRMA supports a federal requirement that companies post information about ongoing clinical trials to a registry to assist patients who might want to participate in a trial. The registry, however, should be limited to hypothesis-testing trials and should not require the public dissemination of confidential commercial information.

In addition, PhRMA supports a federal requirement that companies post the results of completed studies to a national clinical trial results database. Like the registry, the results database should be limited to hypothesis-testing trials, which provide meaningful information that could be used to guide prescribing decisions. Moreover, the database should be limited to information about drug products that have been approved for at least one use, since physicians cannot prescribe drugs that have never been approved and are not on the market.

Postmarket Study Authority. PhRMA supports granting FDA explicit statutory authority to require a post-marketing study if, on the basis of new scientific information obtained after a drug is approved, FDA determines that (a) the drug may be associated with a significant new risk not listed on the current approved labeling; (b) a post-marketing study is necessary to assess the significant new risk; and (c) the information expected to be obtained from the post-marketing study would make a material contribution to the approved labeling for the drug. Moreover, the new authority should be limited to significant new risks associated with an approved use of the drug. Although physicians should remain free to prescribe a drug any way they deem appropriate as a legitimate exercise of the practice of medicine, companies should not be required to

conduct research on a use they have not and do not intend to market. Finally, post-marketing studies can be extremely burdensome for sponsors and, in many cases, may be unnecessary to mitigate risks posed by a drug. Sponsors should have the option to take other equally effective but less burdensome actions (e.g., label change) before being ordered to conduct a post-marketing study.

Labeling Authority. PhRMA supports proposals that give FDA greater authority to require a labeling change when warranted. PhRMA also supports the creation of an accelerated dispute resolution process for label changes that maintains the ability of the sponsor and FDA to engage in a meaningful scientific dialogue but also places time limitations on such dialogue to ensure that new safety information is included on the approved labeling in a timely manner. Finally, PhRMA supports the requirement that FDA review and approve all safety labeling changes prior to implementation within 30 days of submission. This will ensure that the FDA-approved labeling remains the primary source of information about a drug product and that safety labeling changes not subject to the dispute resolution process are implemented in a timely fashion.

Distribution and Use Restrictions. PhRMA supports clarifying FDA's authority to approve drug products subject to certain distribution or use restrictions. However, because distribution and use restrictions create significant limitations on patient access to needed medications, they should be imposed only in exceptional circumstances. PhRMA is concerned that providing FDA explicit statutory authority to impose distribution and use restrictions could lead to the routine use of very onerous restrictions that should be reserved for exceptional circumstances. This not only would interfere with the legitimate practice of medicine but also could unnecessarily limit drug availability, particularly in

rural areas, to the detriment of patients. Consequently, any such authority should be limited so that it can be used only when absolutely necessary to ensure safe use of the product. Finally, distribution and use restrictions applicable to an innovative drug should likewise apply equally to any generic copy of the drug.

3. Specific Concerns with Discussion Drafts

PhRMA wants to work with FDA and all stakeholders to improve the already robust drug safety system in a meaningful way that preserves innovation and patient access. While we believe there are flaws with the REMS proposal in the current discussion draft and would prefer an approach that relies upon more targeted revisions (as discussed above), we are providing the following comments under the assumption that there is a continuing commitment to the REMS structure. These comments are provided in an effort to help ensure the proposed legislation accomplishes its goal of enhancing the drug safety system without impairing innovation or patient access to life-saving medications.

Preemption. The REMS and other discussion drafts contain an express anti-preemption provision stating that nothing in the Act "may be construed as having any legal effect on any cause of action for damages under the law of any State (including statutes, regulations, and common law)."

This anti-preemption provision would undermine the REMS bill's purpose of reinforcing the FDA's control over drug warnings because it would enable each state to require warnings (or punish manufacturers for not adopting warnings) that the FDA *specifically rejected* after determining that they have no basis in science. FDA's role under the REMS process is to ensure that labeling is scientifically appropriate and

justified, and accurately and succinctly communicates all relevant safety information in a manner that neither understates nor overstates the risks for a particular product. While understatement of a risk can hurt patient safety, overstatement of a risk can deter otherwise beneficial and appropriate use of a medicine by patients who would clearly benefit. The anti-preemption provision would undermine FDA's primacy in determining the proper complex balance to strike by permitting state judges and juries – in each of the 50 states – to require (and punish companies for not providing) warnings that FDA has determined through the comprehensive REMS process are unsubstantiated or scientifically unjustified. The result would be conflicting warning requirements that would confuse the public, force manufacturers to choose between violating federal or state law, and frustrate the REMS bill's primary purpose of strengthening the FDA's authority over drug labeling.

The anti-preemption provision also would frustrate the REMS bill's safety evaluation and review process. The regime encouraged by this provision would create a strong incentive for manufacturers to overload the FDA with proposed labeling changes so they can avoid liability under inconsistent state labeling requirements. Under the REMS process, FDA would have to consider each of these submissions under the aggressive timelines set forth in the REMS bill and make a determination whether to accept the proposed labeling -- even if the FDA had previously rejected the same or similar labeling as scientifically unjustified. Repeated consideration of such a flurry of submissions designed principally to avoid liability under inconsistent state standards -- not to protect public health -- would thus divert the scarce FDA resources away from the Agency's principal mission of identifying and evaluating emerging and serious safety

considerations that the Agency has not previously addressed. The Supreme Court has previously ruled that flooding the FDA with unsubstantiated submissions designed only to avoid state liability would significantly frustrate the public safety mission of the FDA. The anti-preemption provisions in the various discussion drafts thus should be removed.

Broad Scope of REMS. The proposal to require a REMS for every newly approved drug or biologic creates burdensome, bureaucratic processes for routine risk management measures, such as Dear Doctor letters and labeling changes. The proposal should be structured in accordance with the current FDA position that, for most medicines, routine risk minimization measures, such as approved professional labeling and routine adverse event monitoring and reporting, would be sufficient to achieve a favorable benefit-risk balance, and thus a specific REMS would not be required. Since these routine risk management measures already are required under the FFDCA, there is no reason to require the submission of a REMS for most drug products. A REMS should be required only when the product poses a clinically important and unusual type or level of risk, and routine risk minimization measures are not sufficient to ensure the product is safe when used in accordance with its labeling.

As currently structured, if a drug sponsor wanted to issue a Dear Doctor letter, for example, it could be required to submit a full-blown REMS assessment and modification proposal to FDA. The sponsor would then have to wait for formal FDA review and the issuance of an "order" before sending its Dear Doctor letter. Clearly, this type of bureaucratic process is not necessary for routine risk minimization measures and could have the perverse effect of delaying the communication of important safety information to healthcare professionals and the public.

While the current proposal includes a provision allowing waivers of the REMS requirement, the standard is so high as to be virtually unattainable. In particular, a waiver may be granted if there is "substantial evidence that the waiver will not pose a risk" to anybody who might use the drug for its approved use. First, the standard requires the applicant to prove a negative, i.e., that the waiver "will not pose a risk." Second, it requires "substantial evidence" to prove the negative, which has been interpreted by FDA as requiring two adequate and well-controlled clinical trials (i.e., Phase 3 trials). Clearly, this hurdle to obtain a waiver will rarely, if ever, be attained. Rather than require REMS for all products with the option of an illusory "waiver," the REMS requirement should be structured so that it is reserved only for those products posing a clinically important and unusual type or level of risk for which routine risk minimization measures are inadequate.

Civil Money Penalties. The REMS discussion draft grants FDA sweeping new authority to impose civil monetary penalties (CMPs) for any violation of the FFDCA. Under the proposal, a person or entity could face fines as high as 10 per cent of a product's annual U.S. sales or $1 million, depending on how long the product at issue has been on the market. These dollar amounts, which could reach tens or even hundreds of millions of dollars, are extraordinary. By contrast, the civil penalties in current law for drug sample diversion are $50,000 for the first two violations in a 10-year period, escalating to $1 million only when subsequent violations in that period, and there is no reference to annual product sales.

These extraordinary penalty levels are especially troubling given the broad and subjective nature of many of the requirements of the FFDCA. For example, an adulteration violation can be based on failure to meet "current good manufacturing

practices," a requirement FDA has asserted is always evolving and that is highly subjective at best. Advertising and promotional violations likewise are notoriously subjective. These extraordinary penalties will create perverse incentives regarding enforcement of the FFDCA and may make it difficult or impossible for a company to defend itself with the threat of massive CMPs hanging in the background. Furthermore, the impact of such high penalties on smaller and mid-sized companies, which may have only one or two marketed products, could be significant.

Submission of Marketing Plans. The REMS discussion draft grants FDA the authority to require, as part of its review of a REMS, submission of the marketing plan for the drug under review. This unprecedented requirement is ill-defined and ill-advised. It is inappropriate for FDA to review a company's internal competitive plans except in the most extraordinary of circumstances. The plans will not provide FDA helpful information to address the challenges of risk management, and will at best divert the agency's attention from the scientific and data driven issues on which it should be focusing.

To the extent that a company's internal plans have any relevance to the REMS requirements, it is only when those plans translate into the actual promotional communications a company makes in the marketplace. FDA already has sufficient tools to address this issue under current law, which requires that all advertising and promotional materials be submitted to the agency. In addition, a new proposal put forward by FDA will create a system for prior FDA review of consumer advertisements. Where those actual promotional pieces are misleading, FDA can take action under its existing enforcement authority and can otherwise consider the communication measures

of a REMS. Moreover, FDA can take enforcement action under the discussion draft if a company fails to meet the requirements of its REMS. Nothing further will be gained by creating a new mechanism for agency review of a company's internal plans.

It is inappropriate for a regulatory body to be charged with routine review of internal business planning documents. FDA has neither the experience nor the resources to review internal market analyses and other components of commercial planning materials on a regular basis. Moreover, by granting FDA the power to revise a REMS based on a marketing plan, the proposal essentially gives the agency the power to review *and approve* these internal company documents. Absent extraordinary and highly compelling reasons, neither FDA nor any other agency should be charged with the extreme measure of overseeing the internal affairs of the private entities it regulates.

Post-Approval Study Authority. The discussion draft gives FDA broad authority to request post-market studies (e.g., observational studies) and post-market clinical trials, both before and after approval. The standard for requiring studies or trials is extremely low and could result in mandatory post-marketing commitments for virtually all drugs, studies which in many cases would likely be unnecessary and a diversion of both FDA and company resources from other more important activities. Under the bill, studies could be required if adverse event reporting is not sufficient to assess a signal of a serious risk or identify unexpected serious risks in unstudied populations (e.g., children, elderly). This standard gives FDA virtually unlimited discretion to order studies because the requirement can be triggered by a single serious adverse event – *or even by no adverse event at all.* For example, FDA could order a sponsor to conduct multiple studies

searching for evidence of a serious adverse event that had never been observed in any population, i.e., an "unexpected" serious risk.

PhRMA believes that studies should be required only when scientifically and medically justified, not based upon administrative whim or the desire to go on adverse event "fishing expeditions." Requiring unnecessary studies will harm innovative research and development activities while generating little useful information for prescribers and patients. The standard should be revised to permit FDA to require a post-approval study only when new scientific information suggests that the drug may pose a significant new risk not adequately reflected on the approved labeling and the information derived from the study is expected to yield meaningful information for patients and prescribers.

In addition, the draft should provide explicit exemptions from the REMS sanctions provisions when studies cannot be completed due to circumstances beyond the sponsor's control. Post-market studies may be impossible to complete for a variety of reasons that have nothing to do with the sponsor's good-faith efforts. For example, a sponsor may experience unforeseen enrollment difficulties due to subsequent approval of a competing product, or the study may no longer be needed because of advancing science. Sponsors should not be subject to sanctions under these circumstances.

Advertising Restrictions. The bill provides FDA with sweeping new authority to limit advertising for prescription drugs in ways that will interfere with the free flow of truthful and accurate information about prescription drugs in violation of the First Amendment. FDA acknowledges that DTC advertising can benefit the public health by "informing patients about the availability of new treatment options and encouraging

patients to see a physician about an illness for the first time." 72 Fed. Reg. 1752 (Jan. 16, 2007). DTC advertising also encourages dialogue between physicians and patients and promotes improved compliance with physician-prescribed treatments. The restrictions that could be imposed under the bill have the potential to harm the public health by reducing or eliminating these public health benefits, particularly with respect to new treatments for patients looking for better options.

Moreover, the standards for imposing the various advertising restrictions in the bill are extremely vague and set a low hurdle for FDA. For instance, a three-year moratorium can be imposed if FDA decides that it is "necessary to protect public health and safety." Likewise, mandatory pre-clearance can be imposed if FDA decides that it is "necessary to ensure compliance with section 502(n)" regarding the disclosure of serious risks. There is no guidance as to when or why a complete ban on truthful and accurate DTC advertising would be "necessary to protect public health and safety" or when or why pre-clearance would be needed to enforce section 502(n), which already is enforceable through the Agency's authority to punish misbranding violations. These standards amount to no standards at all and will permit FDA to impose extremely onerous advertising restrictions virtually at will.

Distribution and Use Restrictions. The bill gives FDA authority to impose distribution and use restrictions when necessary to assure safety. This provision raises several major concerns.

First, distribution and use restrictions create significant limitations on patient access to needed medications. Consequently, they should be imposed only in exceptional circumstances. PhRMA is concerned that providing FDA explicit statutory authority to

impose distribution and use restrictions could lead to the routine use of very onerous restrictions that should be reserved for exceptional circumstances. This not only would interfere with the legitimate practice of medicine but could unnecessarily limit drug availability, particularly in rural areas, to the detriment of patients. The standard for imposing distribution and use restrictions should be raised to help ensure that onerous distribution and use restrictions would be used only when absolutely necessary to ensure safe use of the product.

Second, the bill inappropriately places the responsibility for policing physicians and pharmacists on drug sponsors rather than the relevant federal and state authorities. The bill gives FDA the authority to require individual companies to monitor physicians and pharmacists and enforce compliance with distribution and use restrictions. Although companies sometimes agree to help facilitate compliance with distribution and use restrictions through, for example, education programs, the bill goes far beyond the normal scope of a company's responsibility to monitor the downstream use of its products – and far beyond most companies' capabilities to do so. The bill essentially shifts enforcement responsibilities from the appropriate federal and state authorities (e.g., FDA, Boards of Pharmacy) onto individual companies. It also forces companies to interfere with and regulate both the practice of pharmacy and the practice of medicine. These responsibilities are inappropriate and should be removed from the bill. The new "implementation" requirements not only interfere with the legitimate practice of medicine but also could create increased product liability exposure for sponsors.

"Black Triangle" Requirement. The REMS discussion draft requires, for the first two years after a new drug or indication is approved, that the labeling of that drug

and any DTC advertising include a "unique symbol indicating the newly approved status of the drug or indication." FDA considered a similar requirement in December 2000 — a black triangle on new drugs for three years following approval — and, following a five-year public stakeholder process, abandoned the idea on the ground that the triangle would not be "universally understood, could be confusing to the prescriber (even with a concerted educational effort) and therefore may not serve its intended purposes." 71 Fed. Reg. 3922, 3936-37 (Jan. 24, 2006).

A special symbol is unnecessary because FDA regulations already require the drug label to bear the year of initial approval in the Highlights section. 21 C.F.R. § 201.57(a)(3) and (d)(5). Moreover, the proposed special symbol likely will have no meaning and limited practical value, because it would be included in the labeling of most prescription drugs in the market. Although it must be included in labeling for only the first two years, it is likely that labeling distributed in the first two years will remain in circulation for much longer. Moreover, because the symbol must be included whenever a drug receives approval of a new indication, even drugs that have been marketed for an extended period may be required to bear the symbol. For example, under the proposal, a twenty-year-old anti-fungal medication just approved for a new dermatological condition would be required to bear the "newly-approved" symbol. This expansive and indiscriminate use will dilute the intended value of the symbol. The special symbol requirement thus should be deleted.

Clinical Trial Registry and Results Database. PhRMA generally supports increased transparency but has the following concerns with the discussion draft.

The bill requires companies to submit, in addition to a technical summary of a study, a non-technical summary in lay language that is understandable to patients. The requirement, while well-intentioned, is unworkable. Clinical trial results are complex, nuanced, scientific documents that often cannot be translated easily into lay language. This is particularly true if the results of the study are inconclusive or have statistical limitations. Companies may find it difficult or impossible to translate clinical trial results into "lay language" without losing important details or appearing to make "promotional" claims. This, in turn, could increase a sponsor's exposure to liability for off-label promotion and false claims violations, particularly given the explicit prohibition in the bill against the submission of information that is "promotional." Moreover, consumers already have access to a wealth of information about the proper usage of drug products, including the FDA-approved labeling, company websites, pharmacy medical information pamphlets and from healthcare professionals. Summaries of thousands of clinical trials, many of which may be inconclusive or of limited scientific value, will not add meaningful information to the resources already available. While clinical trial results should be available to patients and consumers, they should be written for a medical audience. The requirement to submit a summary in lay language should be stricken or, at the very least, limited to situations where the study is of significant medical importance.

The bill also imposes criminal penalties against database submissions that are deemed to be "promotional." This is unworkable because neither the bill nor FDA has ever clearly defined the term "promotional." In fact, FDA has taken the position that the dissemination of scientific studies published in peer-reviewed medical journals can be considered "promotional" if distributed by a pharmaceutical company. Clearly, if purely

scientific journal articles written by independent third parties can be considered "promotional," consumer-friendly summaries written by pharmaceutical companies will be subject to significantly heightened risks. Without clear standards defining the term "promotional," companies will face unacceptable risks under the discussion draft simply trying to comply with the posting requirements. Thus, all references to the term "promotional" should be stricken from the bill. At a minimum, companies should not face criminal penalties for submitting "promotional" summaries, particularly lay summaries, unless and until FDA issues clear guidance defining the line between unlawful promotion and non-promotional scientific exchange.

Finally, the discussion draft requires disclosure of irrelevant information about drugs that are never approved or marketed for any use. The purpose of a clinical trial results database should be to provide useful clinical trial information to physicians to better inform their prescribing decisions. If a drug is never approved or marketed, it cannot be prescribed. The results database thus should be limited to information about drug products that have been approved for at least one use and are available for prescribing in the U.S.

Definitions. The definitions of "serious adverse drug experience" and "unexpected serious risk" should be consistent with the definitions of those and similar terms in FDA's regulations at 21 C.F.R. §314.80. As currently drafted, there are significant differences, which will cause unnecessary confusion and could force FDA to revise its regulations. Unless there is a compelling reason for creating differences between the statutory and regulatory language, which is not evident, the statutory definitions should reference FDA's current regulations or reproduce them verbatim.

REMS Decision-Maker. The dispute resolution process does not specify who within FDA must make a final decision nor does it distinguish between different types of disputes. We believe that for significant requirements, such as whether to order a large, complex and lengthy clinical trial, whether to impose burdensome distribution restrictions, or whether to impose restrictive labeling requirements, the final decision should be made at a high level within FDA. These types of requirements not only burden the specific company involved but, more importantly, can have a significant impact on the public health, the availability of drug products and the practice of medicine. Thus, disputes about post-market studies, distribution restrictions and labeling changes should be ultimately resolved at a level no lower than the Director of the Center for Drug Evaluation and Research (CDER) or the Director of the Center for Biologics Evaluation and Research (CBER).

Labeling Changes. The bill exempts labeling changes that could be made with a "changes being effected" ("CBE") supplement from the assessment requirement of the REMS provisions. While likely not intended, the effect of this provision could be to exempt all safety labeling changes from the REMS provisions, since virtually any safety labeling revision can be made with a CBE supplement. We suggest striking this exemption.

D. <u>Critical Path – The Reagan-Udall Institute</u>

The FDA's Critical Path initiative has set forward to improve the efficiency and accuracy of the drug development process through, among other things, the development and validation of new tools and technologies. These objectives, and FDA's approach to achieving them, are something that PhRMA strongly supports. We further support the

funds for this program included in FDA's proposal to reauthorize PDUFA. This funding will permit FDA staff to be directly involved in external activities such as partnerships and consortia that are generating data and information that will create new paradigms for drug development. In return, FDA commits to developing draft guidance in areas related to safety assessment, clinical trial design, and the use of biomarkers. In addition, FDA will participate in workshops and other public meetings to explore new approaches to a structured model for benefit/risk assessment. The results of these interactions will be used to assess whether pilot(s) of such new approaches can be conducted during PDUFA-IV. Collectively, this will lead to new paradigms leading to more efficient and accurate drug development resulting in earlier patient access of important therapies.

The draft legislation proposing the establishment of the Reagan-Udall Institute will build on this foundational funding, and provide FDA a venue to conduct research in many important areas needed to improve the efficiency and accuracy of the drug development process. As such, PhRMA supports the proposal to establish this institute.

E. Pediatric Study Programs

1. History of Pediatric Exclusivity Program

Historically in the U.S., significant disincentives existed to conduct clinical trials for pediatric use (generally speaking, under the age of 16) of a medicine developed primarily for adult use. Among other factors, exposure to product liability and medical malpractice were prominent disincentives. Prior to enactment of the pediatric exclusivity provisions in the Food and Drug Administration Modernization Act of 1997 (FDAMA), there were concerns that many FDA-approved drugs had not yet been clinically tested in

children. For example, about 70 percent of medicines used in children had been dispensed without adequate pediatric dosing information.[1]

Congress responded to the need for more pediatric specific information by providing incentives to encourage manufacturers to conduct pediatric studies of medicines with potential uses as medicines for children. FDAMA included a provision that granted pharmaceutical firms an additional six-month period of exclusivity, known as pediatric exclusivity, upon the completion of studies on the effects of a drug upon children that meet the terms of a written request from FDA. Although FDAMA included a sunset provision effective January 1, 2002, Congress subsequently reauthorized these provisions in the Best Pharmaceuticals for Children Act (BPCA) in 2002. The BPCA sunsets on October 1, 2007, unless reauthorized.

In addition to the BPCA, the Pediatric Research Equity Act (PREA) gives FDA the authority to require studies of drugs for the approved indication only, i.e., when the use being studied in children is the same as the approved adult indication. PREA gave FDA the authority to require manufacturers to conduct pediatric testing for certain new drugs and biologics and produce formulations appropriate for children, e.g., liquids or chewable form tablets. PREA applies to products that are already on the market only if FDA determines that the absence of pediatric labeling could pose significant risks <u>and</u> after it exhausts the possibility of funding the pediatric studies through other public and private sources. In addition, PREA also applies only if the product is likely to be used in

[1] U.S. Pediatric Studies Incentive Led to New Labeling for Nearly 100 Drugs, Impact Report, Tufts Center for the Study of Drug Development, Vol. 7, No. 4, July/August 2005.

a substantial number of children or represents a meaningful benefit over medicines already on the market.

2. Pediatric Exclusivity Program has Greatly Advanced Medical Care of Children

The pediatric exclusivity program has been a tremendous success. According to FDA, the current pediatric exclusivity program has done more to spur research and generate critical information about the use of medicines in pediatric patients than any other government initiative.[2] For example, according to the FDA, since 1997, the exclusivity incentive program has generated labeling changes for 128 products.[3] A recent GAO study found that almost all of the drugs (87 percent) that had been granted pediatric exclusivity under BPCA have had important labeling changes as a result of pediatric drug studies conducted under BPCA.[4] According to GAO, the labeling of drugs was often changed because the pediatric drug studies revealed that children may have been exposed to ineffective drugs, ineffective dosing, overdosing, or previously unknown side effects.[5] According to a February 2007 study published in the *Journal of the American Medical Association (JAMA)*, data for 59 products were submitted to the FDA between 2002-2004. Using the numbers from the labeling information for these 59 drugs, the study found that 34 percent of the time that physicians prescribed the drugs from this cohort

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[2] "The Pediatric Exclusivity Provision, January 2001 Status Report to Congress," FDA, 2001.

[3] Statement of Rear Admiral Sandra Lynn Kweder, M.D., Deputy Director, Office of New Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, Before the Subcommittee on Health, Committee on Energy and Commerce, U.S. House of Representatives, "Programs Affecting Safety and Innovation in Pediatric Therapies," May 22, 2007.

[4] Pediatric Drug Research: Studies Conducted under Best Pharmaceuticals for Children Act, GAO-07-557 (March 2007).

[5] Id.

before 2002, they were making a dosing error or placing a child at risk of adverse events with limited therapeutic benefit. As the article stated, "Administration of safe drugs that work, at an appropriate dosage, is critical to public health."[6]

Further, sponsors have submitted 504 proposed pediatric study requests to FDA, and 341 written requests have been issued by FDA to drug sponsors requesting over 703 pediatric studies.[7] In comparison, between 1990 and 1997, only 11 products were studied in children.[8]

The public health benefits of these developments are undeniable. According to the American Academy of Pediatrics, "Pediatricians are now armed with more information about which drugs work and what doses."[9] Likewise, the *JAMA* study concluded, "...the greatest return of the exclusivity program is the benefits derived in obtaining new information relevant and applicable toward the care of children, and this benefit should not be compromised."[10]

According to the GAO report, the most frequently studied drugs were those to treat cancer, neurological and psychiatric disorders, metabolic diseases, cardiovascular disease, and viral infections. In total, the drugs studied under BPCA are used to treat

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[6] Jennifer Li et al., "Economic Returns of Clinical Trials Performed Under the Pediatric Exclusivity Program," JAMA, February 7, 2007, Vol. 297, No. 5.

[7] Statement of Rear Admiral Sandra Lynn Kweder, M.D., Deputy Director, Office of New Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, Before the Subcommittee on Health, Committee on Energy and Commerce, U.S. House of Representatives, "Programs Affecting Safety and Innovation in Pediatric Therapies," May 22, 2007.

[8] Jennifer Li, op cit.

[9] "FDA Joins Children's Health Groups to Mark Historic Milestone for Pediatric Drugs," FDA Press Release, December 19, 2005.

[10] Jennifer Li, op cit.

more than 17 broad categories of disease in children.[11] The range of conditions studied, the variety of drugs being studied and the nature of the scientific data all confirm that the pediatric exclusivity incentive is working and successfully meeting unmet medical needs in children.

3. Companies Continue Responding to the Incentive as Complexity and Cost of Pediatric Studies Increase

According to the Tufts Center for the Study of Drug Development (hereafter referred to as the Tufts Center), the cost, length, and complexity of pediatric studies have increased significantly since 2000. At the same time, companies have continued engaging in this important research and responding to FDA written requests at very high numbers. The GAO found that most of the on-patent drugs for which FDA requested pediatric studies under BPCA were being studied.[12] This conclusion is supported by the Tufts Center, which found an 84 percent industry response rate to FDA written requests for pediatric studies.[13] This exceeds the 80 percent response rate expected in FDA's 2001 Status Report to Congress.

Scope, Time and Costs of Pediatric Studies Expanded Significantly in Recent Years

From 2000 to 2006, the scope of pediatric studies has expanded significantly. For example, the average number of patients per written request increased 178 percent, while the average number of studies per written request rose 60 percent.[14] Additionally, the

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[11] "Pediatric Drug Research: Studies Conducted under Best Pharmaceuticals for Children Act," GAO-07-557 (March 2007).

[12] Id.

[13] Pediatric Study Costs Increased 8-Fold Since 2000 as Complexity Level Grew, Impact Report, Tufts Center for the Study of Drug Development, Vol. 9, No. 2, March/April 2007.

[14] Id.

time required to complete pediatric studies nearly doubled between 2000 and 2006. Several factors contributed to the lengthening of study times, including increased complexity and scope of studies, as well as the availability of patients, investigators, and facilities, access to FDA staff, to name a few.[15] In addition, the average cost to respond to a written request increased 8-fold from 2000 to 2006.[16]

Number of Efficacy and Safety Studies Grew by 60 Percent from 2000 to 2006; Most Studied New Drugs in Development and New Indications

The cumulative number of pediatric studies completed since 1998 rose from 58 at the end of 2000 to 568 at the end of 2006. Sponsors increased the proportion of efficacy and safety studies – the most expensive and time-consuming studies – from 25 percent in 2000 to 40 percent in 2006. Sponsors are continuing to break new ground – for example, 20 percent of written requests were for new drugs in development, 40 percent were for currently unapproved indications, while 40 percent were for already approved indications.[17]

4. The Pediatric Exclusivity Incentive Should Remain Intact

The pediatric exclusivity incentive has had a tremendous positive impact on the lives of children, but there is much more to be accomplished. For this reason, the current program – which is working well – and its basic features should not be altered. Changes in the current program could reduce the incentive to conduct pediatric studies.

Exclusivity is Not a Guarantee

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[15] Id.

[16] Id.

[17] Id.

It is important to remember that despite the incentive the pediatric exclusivity program has provided, pediatric studies are done at risk. As a preliminary matter, the FDA may determine that a company's studies do not fairly respond to the written request and therefore the company would be denied exclusivity. Further, programs may fail due to technical reasons, lack of sufficient patients, problems with study design, inadequate time to complete studies prior to loss of exclusivity, etc. Even when a company is granted exclusivity, the value of such exclusivity may be diminished (or nullified) for other reasons. Given these factors, Congress should not increase the hurdles necessary to qualify for pediatric exclusivity.

Majority of Medicines Studied by Sponsors were Not in the Top 200 Sellers; Blockbuster Drugs Receiving Pediatric Exclusivity Have Helped to Build the Necessary Infrastructure for Sustainability and Continued Growth of Pediatric Programs

Pharmaceutical companies have pursued pediatric studies for many products that are not top-selling medicines. In fact, less than half of the products that received pediatric exclusivity were in the top 200 selling drugs, according to the Tufts Center.[18] Some of these include medicines for HIV/AIDS, leukemia, anti-infectives, antihistamines and anesthetic drugs. In addition, only about one-tenth of drugs awarded pediatric exclusivity were in the "blockbuster" category.[19]

While blockbuster drugs represent only one-tenth of the drugs awarded pediatric exclusivity, the exclusivity benefits of one blockbuster drug can support pediatric studies for other drugs and can support and expand infrastructure for pediatric drug programs.

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[18] U.S. Pediatric Studies Incentive Led to New Labeling for Nearly 100 Drugs, Impact Report, Tufts Center for the Study of Drug Development, Vol. 7, No. 4, July/August 2005.

[19] Id.

As with drug development in general, higher revenue drugs support the ability of pharmaceutical companies to invest in research for medicines with lower expected revenue. In the case of pediatrics, not only have blockbuster drugs allowed companies to invest in research for lower revenue products, they have also given companies the ability to build pediatric programs and infrastructure over the past decade. Prior to enactment of the pediatric exclusivity incentive, such infrastructure did not exist. It is important to understand that without this infrastructure, which needs to be permanent, it could impact companies' ability to conduct pediatric drug development. Unique expertise is required to develop drugs for use in children, and thanks to the pediatric incentive, companies have made significant investments in building capabilities in this area. As such, maintaining the current incentive structure will be critical to continued research in this area.

According to Dr. Floyd Sallee, M.D., Ph.D., a child psychiatrist and director of the pediatric pharmacology research unit at Cincinnati Children's Hospital Medical Center, "There was no infrastructure for the research before....Drug companies have hired pediatric experts and there is a larger network of expertise to draw from."[20] Dr. Sallee's comments were echoed by an industry expert, Dr. Stephen Spielberg, M.D., Ph.D., "The legislation has encouraged the development of needed infrastructure, highly specialized staffing needed to develop pediatric formulations and to perform pediatric clinical studies."[21] Similarly, the GAO has testified that, "Experts agree that, since

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[20] "Drug Research and Children," FDA Consumer (January – February 2003), http://www.fda.gov/fdac/features/2003/103_drugs.html

[21] Testimony of Stephen P. Spielberg, M.D., Ph.D., before the Senate Committee on Health, Education, Labor and Pensions, Hearing on Pediatric Drug Development, May 8, 2001.

FDAMA, there also has been significant growth in the infrastructure necessary to conduct pediatric studies....The pharmaceutical industry has also increased its capacity to conduct pediatric studies since enactment of FDAMA."[22]

Revenues from top-selling products can support pediatric and adult drug research and development in other "non-blockbuster" areas. "Since research resources are allocated across drug portfolios...these medicines indeed provide the fuel to drive research and development of less remunerative compounds..."[23] Dr. Spielberg continued, "For currently marketed drugs, establishing and maintaining excellent pediatric drug development programs can be driven to some extent by higher income medicines."[24]

Congress has also recognized the relationship between the incentive and development of pediatric research infrastructure. "The [Senate HELP] Committee is aware that the incentives created by the pediatric exclusivity provision have encouraged the drug industry to develop and expand its infrastructure and expertise in the study of drugs in pediatrics."[25]

The pediatric exclusivity incentive must be preserved to ensure that pediatric drug development is not hindered in the face of uncertainty over likelihood of reauthorization and rising research costs. Diminishing or otherwise reducing the value of the incentive, for instance by reducing the exclusivity period or by tiering exclusivity for certain drug products could also create unintended ripple effects across the entire program. While

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[22] S. Rep. No. 107-79 (October 4, 2001).
[23] Id.
[24] Id.
[25] Id.

some have argued the returns received from some products (namely blockbuster drugs) as a result of pediatric exclusivity are not in line with the cost of the studies undertaken, the fact is that blockbuster drugs have created the ability for companies to invest in pediatric programs and infrastructure necessary to conduct research across a company's portfolio. Specifically on the issue of proposals to institute a tiered exclusivity incentive, this structure fails to recognize the basic structure of the pharmaceutical research sector, in which a few high-selling medicines often support the research investment in medicines that are needed but that do not achieve large sales. In fact, research conducted by economists at Duke University found that on average, 7 out of every 10 approved medicines do not recover their average development cost. The authors concluded that companies must rely on a limited number of highly successful products to finance their continuing R&D.[26]

5. BPCA and PREA are Complimentary Programs that Should Remain Connected

BPCA and PREA are complimentary programs that should remain connected. PhRMA would propose eliminating the sunset for both programs or alternatively sunsetting them at the same time. It could be very damaging to the operation of companies pediatric research programs if one program continues without the other. As discussed previously, the pediatric exclusivity provisions have been an overwhelming success, generating more than 120 new pieces of information in drug labeling. At the same time, the pediatric assessment provisions in section 505B of the Federal Food, Drug, and Cosmetic Act have generated new labeling in 40 drug products since

[26] Grabowski H. and Vernon J., "Returns to R&D on New Drug Introductions in the 1980s," Journal of Health Economics, Vol. 13, 1994.

enactment of the legislation in 2003, according to the FDA.[27] Together, these two programs have worked extremely well to generate new information on pediatric uses of drug products, and they should remain linked. In the past, Congress made certain that the PREA study authority remained in effect so long as the pediatric exclusivity incentives also remain in effect. This ensured that the two programs were tied together, and evaluated together. This is the right approach. Given the success of the programs and the complimentary nature of each to the other, there is simply no reason why the two programs should be de-linked. Accordingly, we urge Congress to adopt a mechanism that allows both to be both made permanent or both re-examined in 2012.

PhRMA strongly urges Congress to reauthorize the BPCA and PREA without modification. The increasing rate of industry study proposals and written requests for studies by FDA shows continuing progress, which would be significantly undermined if this important legislation were allowed to expire. In addition, we urge Congress to proceed with caution when considering changes to the incentive that could have unintended consequences to pediatric research.

F. Conclusion

Since its enactment in 1992, PDUFA has brought about tangible benefits to patients, the FDA, and the pharmaceutical industry. FDA's appropriated resources have been augmented by industry user fees, providing the Agency with sufficient

[27] Statement of Rear Admiral Sandra Lynn Kweder, M.D., Deputy Director, Office of New Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, Before the Subcommittee on Health, Committee on Energy and Commerce, U.S. House of Representatives, "Programs Affecting Safety and Innovation in Pediatric Therapies," May 22, 2007.

resources to conduct reviews of new pharmaceuticals in a thorough and timely manner assuring widespread patient access.

The FDA's PDUFA-IV proposal is no exception to this approach, and contains important new provisions and resources to:

- enhance and modernize the FDA drug safety program,
- add a new user fee program to give FDA additional resources to review and provide advisory opinions on direct to consumer television advertisements,
- improve drug development, and
- provide more stable financing for the program.

PhRMA supports FDA's PDUFA-IV proposal, and urges Congress to reauthorize it as rapidly as possible.

The current drug safety system is robust and effective, ensuring that drugs are rigorously tested before they are marketed and closely monitored after approval for any emerging safety signals that need to be factored into the benefit-risk equation. But there is no question that even a good system can be made better. Despite its critical role in monitoring drug safety and protecting the public health, FDA has been chronically underfunded for many years. FDA's most pressing needs, therefore, are for resources to fund its postmarket surveillance activities and a more modernized approach to drug safety that leverages new techniques and resources.

PhRMA believes that the robust drug safety provisions in the PDUFA-IV proposal address all of FDA's drug safety needs. These new provisions, along with FDA's own internal reforms, should be allowed to work to enhance and modernize the drug safety system. We are concerned that adding significant new authorities and a

markedly different review paradigm such as the REMS, may actually be counter-productive. The REMS process creates a complicated and bureaucratic safety oversight system that may not be workable in practice. These additional processes may actually impair drug safety oversight by miring FDA safety officers in unproductive bureaucratic exercises rather than meaningful safety surveillance activities. At the very least, such processes (and hence resources) should be focused on drugs with significant risks, rather than being applied to all products.

If Congress believes that the drug safety enhancements in the PDUFA-IV proposal are not sufficient and that FDA needs additional authorities, this should be accomplished through carefully targeted revisions to the FFDCA. For example, an accelerated label revision process could be added to the Act to ensure that labeling discussions on important safety issues do not extend too long. Significantly, this change and other targeted revisions can be accomplished *without* creating an entirely new bureaucratic maze.

Finally, BPCA, combined with PREA, have been pivotal in creating a positive, sustainable environment for pediatric drug research in the US. The impact of BPCA has been undeniable, with over 128 products labeled with pediatric indications since the start of the program. Given this evidence base, Congress should carefully consider the implications of changing the already-proven structure of these programs before making changes. Particularly, the introduction of exclusivity tiering or exclusivity adjustment will create significant uncertainty in the program, which in turn may reduce the amount of pediatric research that is undertaken. It is also important that PREA remain connected

to BPCA, as the two are inherently linked. As such, PhRMA would propose eliminating the sunset for both programs or alternatively sunsetting them at the same time.

PhRMA wants to work with FDA and all stakeholders to improve key aspects of FDA's programs in a meaningful way that preserves innovation and patient access. We believe that significant strides already have been made with the PDUFA-IV proposal, particularly with regard to drug safety, and we ask you to reauthorize PDUFA-IV as quickly as possible. We also urge Congress to focus on targeted drug safety reforms to address key issues with the existing robust systems, as well as to reauthorize BPCA and PREA as currently authorized.

Mr. PALLONE. Thank you. Mr. Guest.

STATEMENT OF JAMES GUEST, PRESIDENT AND CEO, CONSUMERS UNION

Mr. GUEST. Mr. Chairman and members of the committee, thank you for the opportunity to testify on what is crucial legislation to improve the safety of our Nation's prescription drugs. Consumers Union is the independent, nonprofit publisher of Consumer Reports, with 8 million online and print subscribers and we have been working for a long time to strengthen our drug safety system at the State and national level on behalf of the consumer interest.

Drug safety is not a dry and abstract issue. It is a matter of life and death. In the room today behind me are families and individuals who suffered from what we believe are adverse drug events that could have been avoided, Mr. Chairman, with stronger laws. It is critical that Congress close the gap between the time when drug makers first learn of drug safety problems and when consumers learn this information. These individuals behind me face a lifetime of heartbreak and grief because Congress has not closed that gap and done enough to promote drug safety.

One of those persons behind me is Patricia Slingo, who is described in an ad that Consumer Reports has taken out today, a full-page ad in USA Today, describing her situation, where she was prescribed Vioxx, never told about the heart safety risks that it could have. She ended up in angioplasty stints placed in her heart and bypass surgery. As she puts it, "I can't say for certain Vioxx caused my heart problems, but I wish I would have known what the drug maker knew." And that statement really goes to the crux of the matter before us. The public is not being given the full story about all the potential risks of medications and therefore they can't make informed decisions about their healthcare. We need you, as the committee and the Congress, to significantly strengthen drug safety laws and adequately fund drug safety efforts at the FDA.

My written statement, Mr. Chairman, explains how these measures will help prevent future Vioxx disasters, the uncertainty we are seeing now with the diabetes drug Avandia, and other threats to patient safety. But let me concentrate my comments here on four key points.

First, we strongly endorse your proposal that all phase II through IV clinical trial results be honestly and accurately made public in a timely manner. If there is concern about the integrity of the trial data that would be made public by drug companies, as we have heard from some, you can study and recommend regulations on ways to achieve unbiased, honest reporting. In the interim, though, whether perfect or not, make all results and data public so that the world's researchers can help detect serious problem areas and detect them early rather than well after the fact.

Second, there is great concern that the drug safety division in the FDA has been overshadowed and in some cases ignored by the division that approves new drugs to the detriment of public safety. Again, we urge you to raise the drug safety office's profile, independence, and influence in critical decisions. To help achieve that, you could include the Kennedy-Enzi section 210, which makes public the FDA drug action letter, including a public statement of any

dissents and disagreements about a drug safety. We hope you will also include language on the right of staff to publish in scientific journals, and that you include whistleblower protection for FDA staff who raise safety concerns. We have also long supported legislation by Representatives Tierney and Stupak that would create a separate Office of Drug Safety within the FDA, a focus point within the agency where safety issues can be raised, vetted and acted on. Now, I understand if there is a concern that a completely separate office would slow but, as you have heard, we recommend at the least Senator Grassley's amendment that failed by only one vote on the Senate floor vote. It would give the Office of Drug Safety the power to ask for a safety change on a medication. If the director of the Office of New Drugs disagreed, the commissioner would be required to quickly settle the dispute. This would not slow actions down, but would clearly make someone responsible for safety and resolving these issues.

Third, given the long history of abuses in direct-to-consumer advertising, we recommend that consumers get the most accurate, up-to-date clear information about a drug's benefits and risks. Currently under the voluntary DTC User Fee Program, there is no incentive for a drug company to pay the user fee to have their ad cleared. Consumers deserve the right to have the full information. They should be given the truth, the full truth, and nothing but the truth, and that is what we recommend for this legislation. In the rare cases of drugs with serious potential health dangers, we also support including up to a 3-year temporary delay period on DTC ads as part of the REMS safety tool chest, but that would be a very rare occurrence, but it should be available to the FDA. It is a commonsense consumer protection tool.

Finally, on conflicts of interest, we would urge you to prohibit any conflicts of interest on drug advisory committees. It is critical that the public have faith in the integrity of our prescription drug safety system. They don't today. A survey a few months ago by the Consumer Reports National Research Center found that six out of 10 consumers feel that Congress and the FDA is not doing enough to protect them. The conflict of interest undermines public confidence, so again, we would say let us have a strong requirement here. Have the FDA go out and find the right people and take some time to find them if they need to.

So those are some of our concerns, Mr. Chairman. Again, thank you for your leadership on this and congratulations on the proposals. We look forward to working for their enactment. Thank you, sir.

[The prepared statement of Mr. Guest follows:]

Testimony of Jim Guest
President, Consumers Union, Independent non-profit publisher of
Consumer Reports

before the
Subcommittee on Health
Committee on Energy and Commerce
U.S. House of Representatives
June 12, 2007

On PDUFA, Risk Evaluation & Mitigation Strategies, Clinical Trials, and Advisory Committee Conflicts

Mr. Chairman, Members of the Committee:

Thank you for the invitation to testify on this key legislative initiative to reform the FDA and improve the safety of the nation's prescription drugs.

Consumers Union is the independent, non-profit publisher of *Consumer Reports*.[1] For over two years we have been conducting a Prescription for Change campaign on behalf of state and national laws to strengthen the prescription drug safety system.

This is not a dry and abstract issue: it is a matter of life and death. In the hearing room today are families and individuals who have suffered from what we believe are adverse drug events that could have been avoided if we had stronger laws and a more aggressive safety effort in the FDA. Instead, these individuals – Patricia Slingo, Cathy Harter, Kim Witczak, Eric Swan, Mathy Downing, Marion Goff, Francine Esposito—all face a lifetime of heartbreak and grief because we have not done enough to ensure drug safety.

Ms. Slingo's story is described in an advertisement we ran this morning in USA Today – she took Vioxx for her arthritis pain but did not know about the drug's increased heart risk. She has since had angioplasty, stent placement and ultimately heart bypass surgery. As she puts it: "I can't say for certain Vioxx caused my heart problems, but I wish I would have known what the drugmaker knew."

That statement goes to the heart of the matter before us – the public is not being given the full story about all the potential risks of medications and devices, and therefore they can not make informed decisions about their health care. That is why we need to significantly strengthen our drug safety laws and adequately fund drug safety efforts at the FDA.

We have endorsed the Senate-passed Kennedy-Enzi bill, but hope it can be strengthened in the House. We thank all the Members who have worked on these issues, and have endorsed the Waxman-Markey, Hinchey-Stupak, and Tierney-Ramstad bills and hope their many good features can be included in the final law.

Chairman Pallone, we thank you and strongly congratulate you on the drug discussion drafts before us today: it combines several of the best features of all these other efforts, increasing the level of drug safety without slowing the approval of life-saving drugs.

How Discussion Draft Will Help Prevent Future Drug Safety Tragedies

REMS provisions: This proposal builds on the best provisions in the Senate-passed bill and the Waxman-Markey bill (HR 1561) to give the FDA the power to ensure that when safety issues warrant action, action can indeed be taken. Today, the FDA has limited authority to ensure post-market safety studies are actually conducted, or that labels can be changed quickly. Its enforcement tools are either too drastic or too weak. There is no system to regularly monitor a drug's history over its life cycle, and the adverse events reporting system is ineffective.

The bill would give the FDA an effective tool chest of authorities (Risk Evaluation and Mitigation Strategies or REMS) to give more attention to safety without slowing the approval of new drugs. The tools could be enforced by meaningful civil monetary penalties. As signs of trouble develop—such as the FDA reviewer's initial warning on Avandia—the FDA can use increasingly strong tools to determine if there is fire behind the smoke of warnings and, if so, act to protect the public.

Of particular note, all new drugs will carry for at least two years a symbol indicating their newness. Why? Because most drugs are approved after testing on a couple thousand usually healthy people for a year or less. Statistically, serious adverse effects or long-term injury will not show up before approval. The real test is when millions of people start using a drug over an extended period of time. Several years ago, a patient data monitoring company ran an advertisement in a drug trade press publication read by pharmaceutical industry employees that says it all:

> "How many prescriptions…
>
> "How many weeks in market…
>
> "UNTIL YOU'RE CONFIDENT THAT YOUR DRUG IS SAFE?"

Consumers should be aware of the newness of a drug, so that they are more conscious of the need to report adverse events to the FDA or, if the drug offers relatively little new advantage, they may choose to stay with an older, more tested drug.

The Pallone discussion bill allows the FDA to require disclosure of dangers in advertisements, and in a few rare cases, even allows a temporary moratorium on ads until we know more about the safety of the drug.

It takes about seven years for the average adverse event to be detected, and therefore it is important to periodically review a drug's safety profile. The discussion bill provides for

yearly reviews of the REMS for at least the first three years after approval, and a review on the 7th year. This is an excellent idea because it will force the FDA to review the history of a drug at a point in time when a sufficient amount of data should be available to improve on its labeling and usage.

Another important provision is the use of large databases (section 5), such as Medicare's, to detect short- and long-term safety problems in drugs and courses of treatment. This concept was first offered by former FDA Commissioner Dr. Mark McClellan and by Senators Gregg, Burr, and Coburn in S. 1024. As Dr. McClellan testified before the Senate HELP Committee on March 14, 2007, the use of such database surveillance might have helped detect the increase heart risk from Vioxx within months, rather than years:

> "...according to calculations by Richard Platt (Principal Investigator of the HMO Research Network CERT), electronic and other data actually used to determine a significant association between Vioxx use and serious cardiovascular events took almost three years to detect a statistically significant association, based on limited population data available for analysis at the time. If data from large health plans could have been pooled...as envisioned by this [section 201] strategy, the significant association could potentially have been detected within just several months...."

If this database monitoring system had been in place, it likely would have resolved the heart-risk questions that recently came to light about the diabetes drug Avandia – which has been on the market eight years – much sooner. We hope that as your refine the bill, you make it very clear that the research and patient *de-identified and privacy protected* data that comes out of section 5's public and privately-contracted research is made public and freely available to researchers everywhere.

However, our support of active database surveillance should not be misconstrued that this the sole fix needed for our nation's drug safety problems. The FDA needs the legislative authority of REMS to act on the warning signals it gets from Routine Active Surveillance and Assessment epidemiological studies. Section 5 without the rest of the REMS title would leave us where we are now: lots of signals of problems, and endless delays in dealing with them because of a lack of clear authority to take action.

We also urge that the Members ensure that this important public health project stresses the use of de-identified patient data, and that privacy protections and guarantees in Section 5 be strengthened to ensure that we fully guarantee privacy and individual rights.

No Federal Preemption: We support the discussion bill's recognition that nothing in these FDA drug bills pre-empts state tort laws. Controversy has arisen because the FDA recently added, without proper notice, ability to comment or clear congressional authority, a note in a preamble to a regulation that it believed its approval of a drug pre-empted a range of state tort actions. This note, if given credence by the courts, would effectively prevent consumers from holding drug companies accountable. We find it incredible that an agency which has such a track record in protecting the public against

dangerous products and company misrepresentation of data and safety results would dare to interfere with consumers' only effective recourse -- action in the courts. We hope you take even stronger action, and repudiate the FDA's gratuitous preamble language (as provided in Rep. Hinchey and Stupak's bill, HR 2273, section 6).

PDUFA provisions: Ideally, we would like to see the FDA fully and adequately funded out of the general Treasury. If user fees are needed, then there should be no strings attached, as Rep. Hinchey and Stupak have proposed in HR 2273.

We deeply appreciate the addition of $225 million over five years in new safety money to provide desperately needed resources to conduct post-market approval safety work and modernize the FDA's antiquated computer systems. Because PDUFA triggers some increased general treasury money and now involves safety funding, we strongly support the new idea of including patient and consumer representatives in the negotiations over any PDUFA renewal in 2012. This provision will help ensure more sunshine and public interest in what has been a very closed door private industry process.

Below, I would like to discuss areas of particular controversy or where we hope you can make further improvements on behalf of public safety and a modern FDA.

Culture, Openness, and Scientific Integrity within the FDA; Giving the Office of Drug Safety a Role

Scientific Integrity within the FDA: The Union of Concerned Scientists, the HHS Inspector General, and the Institute of Medicine have all reported serious morale and culture problems within the FDA. Too many staff feel pressured to approve drugs before all safety concerns are reviewed. There also is a belief that they are not free to raise questions or slow the PDUFA-and MDUFMA-driven approval timeframes. Turnover in the FDA is above average for Federal scientific agencies and there have been a number of resignations in protest.[2]

To help address this morale and culture problem, we urge you to include the Kennedy-Enzi S. 1082 section 210 which makes public the FDA Action letter, including a public statement of any dissents and disagreements. The discussion bill seems to make the action letters public, but there is no clear indication as there is in the Senate bill that scientific dissent and disagreement is a normal part of the scientific process and is not to be squashed or hidden, but instead be made part of the public record. Public knowledge of the areas of internal concern—for example, the FDA reviewer's concerns with Avandia—would allow researchers and outside experts to concentrate on answering scientific controversies more rapidly.

We urge you to include language like the Senate's section 501 on the right of staff to be able to publish in scientific journals or speak at scientific forums, but state it more clearly and more simply as contained in HR 1165:

> Officers and employees of the Food and Drug Administration, and individuals

> sponsored by such Administration, may publish in peer-reviewed journals and other scientific publications, and make oral presentations at professional society meetings and other meetings of their peers, unless publication or presentation of the data is subject to Federal export control or national security laws or regulations, or is proprietary information. The right to publish or present such data cannot be waived by any agreement, policy, form, or condition of employment.'

And to make both the Action letter dissent and the right to publish meaningful, we hope that you could include whistleblower protection language within the bill and an explicit prohibition against scientific misconduct or censorship. Rep. Markey's bill, HR 1165, has language that could be considered. The need for increased protection for those who raise safety questions is seen in the June 6, 2007, *New York Times* discussion of the Avandia situation. The FDA has just announced that it is asking for a Black Box Warning on the drug. Yet an FDA staffer who suggested that action a year ago, feels she was discriminated against:

> A supervisor in the drug safety office at the agency said in an interview yesterday that she was rebuked last year after calling for a stronger warning label on Avandia and a competing drug, Actos.
>
> The supervisor, Dr. Rosemary Johann-Liang, said that in March 2006 she approved a recommendation from a safety reviewer at the agency that the drugs be required to carry the strongest warning, a so-called black box warning, because they posed a risk of unusual swelling that could lead to heart failure.
>
> But after officials at the agency who dealt more closely with Glaxo complained, Dr. Johann-Liang said she was ordered to retract her approval of the warning, lost her power to approve such assessments and no longer supervised reviews of the safety of Avandia and Actos.
>
> "This was a very careful review that came to an inescapable conclusion," Dr. Johann-Liang said in the interview. "They decided to act like the review never happened and punish me for approving it."[3]

To further promote the status and integrity of science within the agency, we also urge you to consider including the Senate's provision, as recommended by the Institute of Medicine, for an Office of the Chief Scientist (section 222 of S. 1082).

Of course, all of these provisions should apply to vaccines and medical products, not just drugs.

Giving Status to the Office of Drug Safety: We have long supported legislation by Representatives Tierney, Hinchey, Stupak, and Ramstad (and Sens. Grassley and Dodd) that would create a separate office of drug safety, with actual power to order various safety actions. Today, the office of safety, called the Office of Surveillance and

Evaluation, is a small unit that is overwhelmed and, according to the GAO and IOM, often ignored by the much larger Office of New Drugs (OND). While the OND spends a great of deal time considering safety issues, its prime job is processing new drug applications.

In the Senate bill, there are references to the office of safety and the OND working together to adjust a REMS, but it is a very vague power.

We need a locus, a point of responsibility within the FDA where safety issues can be raised, vetted, and acted on.

If there is concern that a completely separate office would just 'slow things down,' and create a duplicate bureaucracy, there is an easy answer. It is the Grassley Senate floor amendment #1039 that failed by only one vote in the last minutes of debate. Basically, the proposal gives the Office of Drug Safety the power to ask for a REMS change—for example, a study to follow up on the warnings raised in the approval of Avandia. If the Director of the Office of New Drugs disagreed, the Commissioner would settle the dispute within a short time period (say a week). This would not slow actions down, but it would clearly make someone responsible for safety within the agency. Today, the voice of safety is too often lost in the drive to meet PDUFA approval deadlines, and as such, public safety suffers.

Clinical Trial registration:
International effort moving to include Phase 1 trials; US legislation should be supportive.

We strongly support the registration of Phase 2-4 clinical trials language. By public registration of trials as they start, we can help patients find appropriate trials to participate in. But also, by publicly establishing what a trial is to measure, for how long, on how many people, etc., the FDA and researchers will be able to determine whether certain research results may have been hidden or doctored when it is ultimately made public. This was the abuse that occurred in Paxil's trials on use in younger people, and the bill's language would prevent that kind of scientific dishonesty.

The clinical trial registration movement was driven substantially by the International Conference of Medical Journal Editors' call two years ago for registration as a condition of journal publication. On June 4th, the ICMJE announced that beginning with trials commencing after June, 2008, it would also require the registration of Phase 1 trials, "because these studies can guide future research or signal safety concerns." We support this international movement and hope that the legislation would be expanded to registration of Phase 1 trials. While Phase 1 trials involve tests on only a handful of people, they are important, contribute to the statistical base of knowledge, and—when unsuccessful—can save other human beings from undergoing dangerous tests. Dr. Steven Nissen testified before the Senate HELP Committee on November 16, 2006:

> When drugs show serious toxicity in patients, the results are rarely published. Accordingly, other companies subsequently expose patients to closely-related drugs without knowing that their competitors' study of a similar agent showed significant harm. I am aware of a class of drugs where more than a dozen compounds showed serious toxicity, resulting in termination of development, but without a single publication of results. In my view, when a patient volunteers to participate in a drug or device study, there is an implicit moral obligation that the patient's participation will benefit medical science. When studies are not published, we learn nothing from the experiment and make the same mistakes over and over again. [Underlining added.][4]

For the sake of science and for those who volunteer their health in these trials, all trials should be registered, and as quickly as possible, the results made public.

We hope that you can include language that will encourage more initial diversity in clinical trials. All too often, we are testing on middle-aged Caucasians and have little or no understanding of the impact of a drug on other races, older citizens, and in particular, older women. And again, all of these provisions should apply to vaccines and medical products, not just drugs.

Results of Clinical Trials:
House Language Gives Us Certainty that Trial Results will be Public

We strongly support your proposal's requirement that all Phase 2-4 Clinical Trial Results will be honestly and accurately made public in a timely manner, in both a non-technical, unbiased form for the average consumer, and in more detail for the medical and scientific community. This should apply to all medical products tested in clinical trials.

The original Enzi-Kennedy bill looked a great deal like your proposal. But we understand that many in the industry were fearful that the detailed information would be too confusing to the consumer and cause too much uncertainty. We at Consumers Union find that argument insulting.

What is more serious, is that experts at the National Institutes of Health and the National Library of Medicine have expressed concern that some trials are scientifically worthless and in many cases, just promotions or a marketing pitch for the drug studied. As the former editor of *The Lancet* said in 2004, "Journals have devolved into information laundering operations for the pharmaceutical industry."[5] How does the government insure that trial results are honestly presented, when so much of the process has been corrupted?

To try to answer the question of how to honestly present trial results, the Senate bill includes a study and a negotiated rule-making leading to a final regulation 30 months after the bill's enactment that would describe the "what, when, and how" of trial reporting. In the interim 30 months, there will be a link to public data (including the

excellent idea of a link to Section 210's Action Package) "for those clinical trials that form the primary basis of an efficacy claim" or are a Phase IV post approval safety trial.

These Senate provisions could be a major problem. All trials should be made public, not just those that are the 'primary basis of an efficacy claim.' And after the 30 months of study in the Senate bill, we have no idea what will be made public, how quickly, and in what detail. We see no guidance to these questions.

We urge you to support the House discussion language on clinical trial results. If there is concern about the integrity of the data being made public, study that issue over 30 months, and provide for future regulations to ensure the honest presentation of data. But in the interim, don't give up on your bill's requirement that all Phase 2-4 trials must be public in a reasonable period of one to two years. In the interim, whether perfect or not, make the data public so that the world's researchers can help detect the areas where there are problems.

We also urge you to make public observational studies conducted by drug companies. While these are not the 'gold standard' that randomized clinical trials are, they can provide incredibly useful information to physicians and researchers -- the recent case of Bayer's Trasylol observational study, which found an increased risk of death, serious kidney damage, etc., but which was not volunteered to a recent FDA Advisory Committee meeting, is a prime example of the public value of these studies.[6]

Moratorium on Direct-to-Consumer Advertising as Part of REMS Tool Chest

Although complete safety risks are often unknown for years after approval, pharmaceutical companies invest huge amounts in the immediate promotion of approved drugs, including billions of dollars in Direct-To-Consumer (DTC) advertising. We have seen, too many times, the devastating effects of such DTC advertising. At least one study has commented on how DTC advertising contributed to the overuse and misuse of Vioxx by both consumers and physicians, which led to an unnecessary increase in the number of people at risk of heart attack and stroke.[7]

> [Vioxx] was the most heavily advertised drug to consumers in 2000 and retail sales quadrupled from 1999 to 2000....In 2003, Pfizer spent $87.6 million promoting celecoxib directly to consumers. Recent data highlight that marked increases in COX-2 inhibitor use occurred primarily among patients at low risk of adverse events from less expensive non-steroidal anti-inflammatory drugs....This inappropriate increase in COX-2 inhibitor use among patients for whom NSAIDs could be used accounted for more than 63% of the growth between 1999 and 2002. That this growth was due solely to DTCA is, again, unlikely, but Dai et al describe succinctly the important role that DTCA probably played in this trend—a trend that may have resulted in as many as 140,000 serious adverse cardiovascular events.[8]

In addition to the safety concerns, DTC advertising of Vioxx increased costs to consumers and health plans alike, which were paying significantly more for a new drug that added little or no benefit.[9]

Some defend the use of DTC advertising, asserting that it promotes patient-physician dialogue and increases awareness of diseases and treatments. One study shows, however, that these ads are rarely educational; while many advertisements gave the name of the drug and the condition being treated, very few provide any additional health information on alternative treatment of the condition.[10] The study reports that out of a possible 11 educational codes (specific educational points), the average number of codes present in advertisements was 3.2. Despite the lack of truly educational information in DTC advertising, consumers tend to believe the pharmaceutical industry's message that only the safest and most effective drugs appear in advertisements.[11] This is particularly dangerous given the fact that the goal of this advertising is to sell a costly product that can potentially have serious safety risks.

Although the perception is that only the safest and most effective drugs are advertised, a revealing poll by PricewaterhouseCoopers reported in January 2007 "that 90 percent of consumers and those involved with the industry do not think that direct-to-consumer advertising provides complete and useful information, while 40 percent of pharma executives thought that it does." This implies that a majority of drug company executives do not believe their own ads provide complete and useful information. Although therer are frequent problems with the accuracy and fairness of ads, *Consumer Reports* has carried a number of stories about how the FDA seldom acts against misleading and false ads, how the level of warnings and penalties has declined, and how some companies have repeatedly violated the truthful advertising regulations.[12]

As a part of REMS, the proposed bill gives the FDA authority to require the pre-clearance of advertisement to ensure specific disclosures of a serious risk listed in the labeling of the drug (REMS discussion bill, pages 15-18). In light of the promotional nature of DTC advertising and the long history of abuses in DTC advertising, and given that such advertising strongly influences consumers, Consumers Union recommends a requirement that **all** advertisements,[13] including the growing use of ads in the Internet and other non-traditional sites, be pre-cleared by the FDA for accuracy and honesty.[14]

We believe that if you provided an automatic, substantial penalty for any advertisement found to be misleading or false, companies would seek pre-clearance, they would use the new voluntary DTC user fee program, and the FDA would be able to prevent false and misleading ads, something it has failed to do under the existing process.

In addition, in those extremely rare cases of drugs with serious potential of danger, the REMS process allows the FDA to impose a three-year moratorium on DTC advertising for drugs. Given the amount of influence this type of advertising has on consumers, and given the potential serious adverse drug reactions that may occur years after approval, Consumers Union supports including up to a three-year moratorium on DTC advertising as part of the REMS safety tool chest.[15]

We hope that you will encourage the FDA to require the inclusion of a 1-800-FDA number in all DTC and other drug ads where consumers can report adverse drug reactions.[16] Currently, most consumers probably have no idea that there is an adverse event reporting system or how to participate in that process. Adding a toll-free number to all drug ads could help improve the level of information on areas of safety trouble.

Ethics in FDA Advisory Committees:
Improvement over Senate language; zero conflict-of-interest policy urged

The Senate-passed bill does almost nothing to address an area of great controversy: FDA Advisory Committee members who are ethically conflicted. There are cases where the votes of ethically conflicted Advisory members made a difference in the outcome of a drug-safety issue.[17] But mostly, allowing conflicted members to vote casts a cloud over some of this expert advice. A recent poll from the Consumer Reports National Research Center found that six in 10 consumers disapproved of allowing doctors and scientists with a conflicting financial interest to participate on advisory boards, and 84 percent of consumers agree that drug companies have too much influence over the government officials who regulate them.

The discussion bill is much stronger than the Senate bill, in that it permits the FDA to grant only one waiver per meeting to permit a conflicted expert to participate in the Advisory Committee process.

The FDA itself has recently moved to exclude from Committees those with more than $50,000 in conflict, and to permit those with less than $50,000 to participate, but not vote. The problem is, the act of being on the Committee is where the socialization and influencing occurs, and transcripts have shown one or two Advisory Committee members can dominate deliberations even when they cannot vote because of a conflict.

We believe you should legislate a zero-conflict policy. If an individual is conflicted or had a financial relationship in the last 36 months, they could testify before the Committee like any other citizen, but not participate as a member of the Committee. Opponents of this change will say that there are not enough experts in a field who lack such conflicts. We don't believe the FDA has tried hard enough to find academic or NIH-funded researchers and other experts who are not conflicted.

We urge you to require the aggressive recruitment of non-conflicted experts in a wide diversity of fields (epidemiology, toxicology, statistics, etc.). To remove doubts of integrity problems, we hope you will codify a no-waiver policy: if an individual is conflicted, they cannot participate in that session of the Advisory Committee. If there is concern that this would create a shortage of experts, phase this zero tolerance requirement in over the next five years, while the FDA conducts a true search for conflict-free experts.

Also on the issue of improving Advisory Committees, there has been a history of FDA expert staffers who have been critical of a drug being considered by a Committee actually

being prohibited from addressing that Committee. We hope you will include language that gives any FDA staffer who requests time to make a presentation, the right to do so without retaliation.

MDUFA

The Draft Discussion version of the Medical Devices User Fee Act (MDUFA) is a clear improvement over the MDUFMA bill that was negotiated by device companies and the FDA and included without any revisions in the Senate bill. We know that the Senate received the negotiated bill too late to be able to focus on it before passage, and we congratulate you for the improvements you made. We support your efforts to maintain the already very speedy process for medical devices [80% of 510(k) reviews completed within 90 days, for example].

We strongly support your efforts to question the 510(k) process, which is used for 98% of medical device reviews. Although the 510(k) review is limited to products that are "substantially equivalent" to devices already on the market, the FDA defines "substantial equivalence" to include products made of completely different materials and using completely different technologies – not at all similar or equivalent as most of us would define those terms. There is reason to be very concerned that implanted medical devices are being cleared for market through the 510(k) process, often without the FDA requiring or reviewing clinical trials. This concerns us because clinical trials are almost always necessary to determine if a product is truly safe and effective. And, it is important to note that these products are usually not available through Medicare, Medicaid, or most insurers until clinical trials prove that they are safe and effective. In other words, CMS and the health insurance companies have higher standards than the FDA, and most consumer will not benefit from quicker approvals because the proper testing has not been completed that would make sure that these products are safe and effective, or to meet criteria that would make them reimbursable through insurance.

One other device issue, we commend the Members of the Committee, such as Rep. Doyle, Dr. Burgess, and others, who are working on efforts to establish a unique device identification number for medical devices—a key step to being able to form registries that can be used when there is the need for a recall or to report adverse events.

Help for Consumers

Finding a full set of objective data about the effectiveness and safety of a drug can be like finding a needle in a haystack. The FDA is trying to improve its website for consumers, but we hope you will include S. 1082's section 209 that pulls all the information about a drug into one website.

Conclusion

Again, we thank you for your hard work on this key health safety issue, and we look forward to working with all of you on the enactment of this important legislation.

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[1] Consumers Union is a nonprofit membership organization chartered in 1936 under the laws of the State of New York to provide consumers with information, education and counsel about goods, services, health, and personal finance. Consumers Union's income is solely derived from the sale of Consumer Reports and ConsumerReports.org, its other publications and from noncommercial contributions, grants and fees. In addition to reports on Consumers Union's own product testing, Consumer Reports and ConsumerReports.org, with approximately 6.5 million combined paid circulation, regularly carry articles on health, product safety, marketplace economics and legislative, judicial and regulatory actions that affect consumer welfare. Consumers Union's publications carry no advertising and receive no commercial support. EXPERT • INDEPENDENT • NONPROFIT®

[2] In testimony to the Senate Finance Committee on November 18, 2004, Dr. David Graham, associate science director of the Office of Drug Safety at the FDA, alleged that FDA officials attempted to suppress and delay results regarding a study which concluded that individuals taking Vioxx had an increased risk of heart attack and stroke. In the same testimony, Dr. Graham mentioned a similar experience held by Dr. Andrew Mosholder, senior epidemiologist at the FDA, whose concerns that Paxil increased suicidal behavior in children were dismissed by higher FDA authorities. In August 2006, the Union of Concerned Scientists (UCS) released their survey of the FDA; their findings echoed those reported by the Office of Inspector General (OIG) in 2003. In response to the question: "Have you ever been pressured to approve or recommend approval for an NDA despite reservations about the safety, efficacy, or quality of the drug?" 41 respondents out of 217 Center for Drug Evaluation and Research (CDER) staff (nearly 19%) answered "yes." Nearly one-fifth (18.4 percent) said they "have been asked, for non-scientific reasons, to inappropriately exclude or alter technical information or their conclusions in a FDA scientific document."

[3] Stephanie Saul & Gardiner Harris, "Diabetes Drug Still Has Heart Risks, Doctors Warn," NYT, 6/607.
[4] "Clinical Trial Registration, Looking Back and Moving Ahead," C Laine, et al. JAMA, June 4, 2007.
[5] PLoS Medicine, May 2005, Richard Smith, "Medical Journals Are an Extension of the Marketing Arm of Pharmaceutical Companies."
[6] FDA Public Health advisory, Feb 8 and Sept 29, 2006.
[7] Dai C, Stafford RS, Caleb GC. National Trends in Cyclooxygenase-2 Inhibitor Use Since Market Release: Nonselective Diffusion of a Selectively Cost-effective Innovation. Arch Intern Med. 2005; 165: 171 - 177.
[8] Matthew F. Hollon, MD, "Direct-to-Consumer Advertising, A Haphazard Approach to Health Promotion," JAMA, April 27, 2005, p. 2030.
[9] Ibid.
[10] Bell RA, Wilkes MS, Kravitz RL. The educational value of consumer-targeted prescription drug print advertising. J Fam Pract 2000;49:1092-1098.
[11] Bell RA, Kravitz RL, Wilkes MS. Direct-to-consumer prescription drug advertising and the public. J Gen Intern Med 1999;14:651-657.
[12] See, for example, Consumer Reports, February 2003, "Free Rein for Drug Ads?"

[13] We note that the voluntary review/user fee provision in the Senate-passed bill and the discussion PDUFA bill define DTC television ads as those less than 2 minutes in length. Recently, there has been controversy about a 2.5 minute ad on a drug which has had safety issues. We see no reason to limit the definition to 2 minutes.
[14] DTC on the InterNet is growing rapidly, and is estimated to be $1.3 billion in 2008. As research firm eMarketer said August 18, 2006, "The spending increase is spurred by federal regulatory crackdowns on pharmaceutical advertising, and the fact that 31.6 million Americans turn to the Internet first for health care information."

[15] "The Court has developed a four-pronged test to measure the validity of restraints upon commercial expression. Under the first prong of the test as originally formulated, certain commercial speech is not entitled to protection; the informational function of advertising is the First Amendment concern and if it does not accurately inform the public about lawful activity, it can be suppressed. Second, if the speech is protected, the interest of the government in regulating and limiting it must be assessed. The State must assert a substantial interest to be achieved by restrictions on commercial speech. Third, the restriction cannot be sustained if it provides only ineffective or remote support for the asserted purpose. Instead, the regulation must "directly advance" the governmental interest. The Court resolves this issue with reference to aggregate effects, and does not limit its consideration to effects on the challenging litigant. Fourth, if the governmental interest could be served as well by a more limited restriction on commercial speech, the excessive restriction cannot survive. The Court has rejected the idea that a "least restrictive means" test is required. Instead, what is now required is a "reasonable fit" between means and ends, with the means "narrowly tailored to achieve the desired objective." Central Hudson Gas & Electric Co. v. Public Service Comm'n, 447 U.S. 557 (1980). Quote from http://caselaw.lp.findlaw.com/data/constitution/amendment01/17.html

[16] Section 9 of the Best Pharmaceuticals for Children Amendments of 2007 calls for the issuance of a rule on the 1-800 adverse event reporting number, and this section could be expanded to cover all drugs advertisements in all media.

[17] Although certain FDA experts have been refused permission to testify at advisory committee meetings, many outside scientific experts are free to participate in such meetings despite outstanding conflicts of interest. For example, at the February 2005 joint meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee to discuss the safety of cyclooxygenase-2 (COX-2) inhibitors, it was disclosed that 10 of the 32 voting panel members had financial associations with the manufacturers of these drugs (such as the receipt of consulting fees or research support). All 10 members were issued general waivers that allowed them to participate in the meeting. 28 out of the 30 votes cast by these 10 members favored marketing of Bextra, Celebrex and Vioxx, whereas only 37 out of the 66 votes cast by the remaining 22 members favored marketing of these drugs. If the 10 panel members with conflicts of interest had not participated in the meeting, the committee would have voted to remove Bextra from the market, and to keep Vioxx from returning to the market (Merck voluntarily withdrew Vioxx from the market in 2004). Instead, due to the inclusion of the votes from the 10 conflicted panel members, the committee voted to keep these drugs on the market. The FDA consequently announced that it had asked Pfizer to voluntarily withdraw Bextra from the market, which it did in April 2005, two months after the advisory committee meeting. Vioxx remains off the market today. Sources: Center for Science in the Public Interest. Conflicts of interest on COX-2 panel. February 25, 2005. (Accessed October 30, 2006, at http://cspinet.org/new/200502251_print.html.); Harris G, Berenson A. 10 Voters on panel backing pain pills had industry ties. New York Times. February 25, 2005.

Mr. PALLONE. Thank you. Mr. Ubl.

STATEMENT OF STEVEN UBL, PRESIDENT AND CEO, ADVANCED MEDICAL TECHNOLOGY ASSOCIATION

Mr. UBL. Good afternoon. I am Steve Ubl, president and CEO of AdvaMed, which is the Advanced Medical Technology Association. I would like to thank you, Mr. Chairman, Ranking Member Deal and other members of this subcommittee for the opportunity to provide our views on MDUFMA.

Reauthorization of MDUFMA is critically important to public health and safety and ensuring FDA is on sound financial footing. I would like to commend you and the subcommittee for including the FDA industry agreement in the discussion draft, and for its critical role in developing the original proposal back in 2002, and for the restructuring of the program that occurred in 2005. The program has made an immense difference to FDA, to industry and to patients. And without your support, we would not be where we are today. However, we do have concerns with the discussion draft, which, in our view, if not address would jeopardize our support for the underlying measure.

First, as we read the preemption language contained in the initial draft and in the chairman's mark, we are concerned to the degree that it would threaten our ability to support the overall bill, the reason being the existing statutory preemption provided for medical devices is absolutely critical to ensuring that FDA's expert and uniform regulatory regime will not be undermined by divergent State requirements. This uniform and predictable regime is critical for innovation for developing the most novel treatments for the most dangerous diseases and for maintaining the flow of venture capital to small firms. And those concerns are reflected in my written testimony.

Essentially, what the draft would do is allow for State courts, State agencies and State legislators to substitute their views or second guess FDA's determinations around safety and effectiveness. I should point out that we very much appreciate that, in the most recent draft, we think you are trying to narrow the scope of this provision. But I would just like to point out by just referencing the clinical trials section of the bill. You are implicating the underlying statute relative to devices. So we view any insertion of ambiguity in this area as highly problematic.

With regard to third-party inspections, we are disappointed that the program was essentially dropped in the discussion draft. In our view, the Third-Party Program should be a win/win for FDA, for the public and for industry. It benefits industry because it reduces the number of duplicative and costly inspections by numerous foreign governments and the FDA. And as Dr. Lutter testified, it benefits the FDA because the agency currently inspects facilities once every 5 years, so it enables the agency to get inspection reports it otherwise would not get to get target resources where problems are most likely. There are many misunderstandings about Third-Party Program and I would like to emphasize a few key protections that are included in the agreement as adopted by the Senate.

None of the FDA inspectional authorities are reduced in any way. FDA can inspect a facility at any time and continue to receive

third-party inspection reports whether FDA inspects the facility or not. FDA credits the third-party inspectors and also inspects the inspectors on a regular basis. FDA can disqualify an inspector at any time, and a company can continue to participate in the program only if it maintains a clean inspection record. In our sense, if the committee leaves the program in its current unworkable form, FDA will be deprived of valuable information that it would otherwise have to make decisions for the public health.

With regard to pediatric medical devices, we support the goal of increasing access to pediatric devices, and I want to commend Congressman Markey and Congressman Rogers for their leadership in this area. However, in order for a pediatric bill to truly be successful in increasing the number of studies, we believe there should be a careful balance of carrots and sticks. Unfortunately, the current draft is virtually all stick and no carrot. The bill lacks any significant financial incentives to provide device companies incentives to conduct pediatric trials. Similar incentives on the drug side have been estimated by HHS to be worth billions of dollars. And they have worked. Those incentives have produced numerous additional trials.

In terms of the stick side of the equation, the bill gives FDA the authority to prohibit access to a device that was developed for an adult or general use, if the agency foresees a potential pediatric use, until such time as the sponsor agrees to conduct a pediatric study. It could take months to negotiate such a study and during that time, patient access to the device in question would be denied. The bill could be improved in our view by providing an expedited waiver process to resolve such disagreements between a product sponsor and the FDA, when in the view of the sponsor, it would be impossible to conduct a trial due to lack of information about the target population or difficulty enrolling patients.

We are also concerned with one aspect of the clinical trial registry provision, the requirement to disclose information on a clinical trial before the device is approved. Unlike drug companies, patents provide only limited protection for device companies, because it is often easy to engineer around a patent for a device. Clinical trial design is critical intellectual property for device companies. If a company's trial design is known to competitors before the device is approved, a competitor can drastically shorten the period of market exclusivity or even beat the originator company to market. We recommend the approach taken in the Senate to require device trial registry, but to delay public disclosure data until the device is cleared or approved by FDA.

In summary, AdvaMed strongly supports reauthorization of MDUFMA. We have had a number of concerns which we have outlined. We ask that you consider these changes going forward, and I appreciate the opportunity to provide my views.

[The prepared statement of Mr. Ubl follows:]

STATEMENT OF STEPHEN J. UBL

AdvaMed, the Advanced Medical Technology Association, represents more than 1,600 medical technology companies, affiliates, and subsidiaries. Our members develop and manufacture medical devices, diagnostic products and medical information systems that represent nearly 90 percent of the health care technology products

purchased annually in the United States, and nearly 50 percent of those purchased around the world. AdvaMed members range from the largest to the smallest medical technology innovators and companies. More than 70 percent of AdvaMed's core members have less than $30 million in sales annually. AdvaMed is pleased to offer this written testimony on behalf of our members.

AdvaMed believes that the reauthorization of the Medical Device User Fee and Modernization Act (MDUFMA) is good for the public health. It will facilitate the timely and effective review of new medical technologies and bring them to patients as soon as those products can be shown to meet the necessary rigorous FDA requirements. It also ensures that FDA's medical device program will be on sound financial footing. FDA's device program needs sufficient funding to do its job in a timely way, and this bill will ensure that the agency has that funding for the next 5 years. However, we have serious concerns that other provisions in the proposed discussion drafts will not serve the public health and instead will undermine the intended impact of user fees and FDA's authority to ensure safe and effective devices.

The constructive goals that emerged from FDA and industry discussions to improve medical device regulation are frustrated by the proposed preemption section that would overturn previous clear Congressional intent and court precedent and elevate individualized state decisions over FDA's expert science-based determinations of product safety and effectiveness. On this issue, we have great concern that the draft not only harms the agency's ability to fulfill its mission to safeguard public health, but also disincentivizes research and development of life saving technologies and diminishes patient access to beneficial technologies. This represents a substantial step back and will cede our nation's leadership in health care innovation. Inclusion of the proposed preemption section may jeopardize industry support for the legislation.

The following summarizes our concerns with the proposals and identifies areas that we believe members of the Subcommittee should examine closely in order to further the public health.

LIMITATION ON FEDERAL PREEMPTION

Section 108 of MDUFMA, which purports to be a "rule of construction," is (1) unnecessary and (2) damaging to medical device innovation and FDA's authority. Specifically, section 108 states "Nothing in this Act or the amendments made by this Act may be construed as having any legal effect on any cause of action for damages under the law of any State (including statutes, regulations, and common law)." It is hard to understand the point of the inclusion of this language in the proposed House bill except as an attempt to create ambiguity regarding the preemptive effect of fee-based agency actions, including approval of premarket applications (PMAs), and to deconstruct the clear Congressional expression of preemption included in the 1976 Medical Device Amendments. Consideration of an issue that would so fundamentally change the FDA regulatory structure should not be included in a bill designed to reauthorize the hiring of additional reviewers at the agency, especially given the importance of reauthorizing the bill before expert reviewers at FDA are notified that the funding, and therefore their jobs, may be in jeopardy.

Manufacturers (and their third party sources of capital that fuel further research and development) require a level of certainty that they will not be subject to state tort liability after spending the vast amounts of time, money, and other resources to adhere to stringent FDA requirements for PMA devices and to obtain FDA's full safety and effectiveness approval of a PMA device. Whether or not section 108 of MDUFMA is an attempt to muddy the waters regarding the preemptive effect of PMAs and device specific reviews, we believe it could have that effect and for that reason should be struck from the proposed House MDUFMA legislation.

Express preemption for medical devices is governed by section 521 of the Federal Food, Drug, and Cosmetic Act (or the FDCA), which expressly preempts state requirements that are "different from or in addition to, any requirement applicable under . . . [the FDCA] to the device, and which relate "to the safety or effectiveness of the device or to any other matter included in a requirement applicable to the device under" the FDCA. According to the House Committee Report for the 1976 Medical Device Amendments, section 521 was included in the 1976 Amendments because consistency in requirements for medical devices was considered necessary to avoid unduly burdening interstate commerce.

Device specific reviews, such as a PMA, entail a comprehensive review of safety and effectiveness by FDA's expert scientists, physicians and other analysts. The PMA process established by the 1976 amendments required the most exacting review for the riskiest devices, those in class III. Additionally these devices were of the most concern, and included those which are either for use in supporting or sus-

taining human life, or are of substantial importance in preventing impairment of human health or present an unreasonable risk of illness or injury. The safety and effectiveness of class III premarket approval devices must be determined with respect to the persons for whom they are intended, with respect to the labeled conditions of use and by weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use.

The PMA process is a rigorous, device-specific FDA review as has been recognized by the courts. To obtain PMA approval, a manufacturer must, among other things, submit full reports of investigations that provide a reasonable assurance of the safety and effectiveness of the class III, PMA device, typically one or more clinical investigations. Breakthrough PMA devices normally are reviewed by an outside panel of experts. The amount and type of data necessary to meet the PMA approval standard of a reasonable assurance of safety and effectiveness requires expert scientific analysis that Congress long ago assigned to FDA and which the agency is uniquely qualified to render. FDA has vigorously advocated preemption in defending its role in determining the safety and effectiveness of devices in recent years.

A substantial majority of courts, including Federal circuit courts, have held that the PMA process is the type of device specific review entitled to preemptive effect over state tort claims under section 521 of the FDCA. Nonetheless, there is a small minority of courts that have reached a different conclusion, including one Federal circuit court. The Supreme Court has not directly addressed the question, thus some uncertainty remains despite the majority consensus favoring preemption in the Federal circuit courts.

In sum, elevating individualized state actions and decisions through tort lawsuits over FDA's expert determination not only undermines FDA's authority regarding product-specific determinations, such as the requirements necessary for PMA approval and adequate device labeling, but also diverts resources from research and development to litigation and insurance. The PMA process applies to the approval of the newest, riskiest, most complex, and some of the most transformative and beneficial devices developed. Innovation leads to earlier disease detection, less invasive procedures, and more effective treatments. The cost of section 108 will be an unnecessary unsettling of the law and resulting additional uncertainty that will likely discourage investment and innovation and delay or deny patients access to devices.

Omission of Third Party Inspection Program Improvements

The MDUFMA discussion draft fails to address the problems currently plaguing third party inspections, a statutorily authorized program widely recognized as falling short of its potential to improve the inspection process and free up agency resources. AdvaMed was pleased to work with FDA and others in industry to design improvements to the FDCA to both encourage more participation and streamline the currently burdensome third party inspection program. We are extremely disappointed that these much needed improvements were not included in the House bill.

The reality of the situation is that FDA does not conduct inspections as often as they would like. In fact, they inspect facilities every 6 years on average rather than every 2. So to reject a streamlining of this process that allows FDA to better focus their resources where they are most needed is short-sighted at best. In fact, the agreement reached by industry and FDA ensures that more, not less, information about facilities will be made available to FDA. And at any time, FDA can choose to pursue its own inspection of any facility.

The changes included in the FDA/industry agreement are designed to streamline the process but do not change in any way the strong conflict of interest prohibitions for industry and third party inspectors. For example, the agreement contains provisions that would simplify the eligibility criteria and process by which establishments request an inspection by accredited parties. Those changes were included in the Senate-passed version of the reauthorization. For example, the owner or operator of an establishment is required to submit a notice to FDA that identifies, among other things, the most recent inspection and its classification. Establishments for which FDA classified the most recent inspection as "official action indicated" would be ineligible for a third party inspection and, unlike under current law, could not submit a petition seeking such an inspection. The Senate bill also eliminated an eligibility requirement that was impractical to satisfy, namely that the owner or operator submit to FDA a statement that the government in a foreign country where the device is, or is intended to be, marketed recognizes an FDA or third party inspection.

Another important change to the program is the elimination on the number of times a company can use a third party inspection. Currently, a company is limited

on the number of times it may use a third party inspector to two times. After two third party inspections, FDA must conduct an inspection. The Senate bill eliminates this limitation and allows a company to continue to use third party inspectors as long as the company maintains a good inspection record. Although this limitation is removed in S. 1082, the statute would require that an establishment must continue to have its inspection reports classified as compliant to continue participating in the program. Under current law, if a manufacturer received a noncompliant inspection from an accredited third party, the company could appeal to the Secretary to remain in the program. This provision is removed from S. 1082.

The authority to conduct inspections at any time remains at the discretion of the FDA. The MDUFMA agreement and the Senate bill allow FDA to consider the goals of international harmonization of quality systems standards thus streamlining overlapping international inspection requirements. Specifically, it would allow FDA to accept international standards reports of certifications, thus providing the Agency the opportunity to receive additional information on a facility so they can focus their resources where they see the most risk. This is another provision that was omitted from the House discussion draft.

The failure to include these process improvements threatens the tenuous existence of the current third party inspection program.

REQUIREMENTS FOR UNIQUE DEVICE IDENTIFIERS FOR ALL IMPLANTS

The proposed amendment that would require FDA to establish a medical device registry and unique identification system for medical device implants represents a broad expansion of current law without delineating any criteria to govern which implants would be subject to the unique identifier requirements, i.e., it is not risk-based and encompasses all implants regardless of their risk. Under the existing authority of §510(e) and 502(o) of the FDCA, FDA is currently developing regulations for a system of unique device identification for all medical devices. Also, FDA currently has authority to require tracking for the useful life of any class II or class III device the failure of which would be reasonably likely to have serious adverse health consequences, which is intended to be implanted in the body for more than 1 year, or which is life sustaining or life supporting and is used outside a user facility. FDA considers the following factors in determining whether a tracking order will be issued: likelihood of sudden, catastrophic failure; likelihood of significant adverse clinical outcome; and the need for prompt professional intervention. The agency has issued tracking orders for a number of devices including abdominal aortic aneurysm stent grafts, cardiovascular permanent pacemakers and electrodes, mechanical replacement heart valves, and silicone gel-filled breast implants.

The proposed identification and registry system would be a wholesale and unnecessary expansion of the present system. It could include devices not likely to have catastrophic failures or that are only implanted short term. For example, under the proposed language, sutures and dental implants would be covered. In sum, the proposed new UDI and registry requirements are duplicative and an unnecessary and unduly burdensome expansion of the current system without real public health benefit.

AVAILABILITY OF PEDIATRIC MEDICAL DEVICES

The device industry is committed to the goal of providing children access to life-saving, life-enhancing medical devices, and we commend Representatives Edward Markey and Mike Rogers for their work on the Pediatric Medical Device Safety and Improvement Act of 2007. AdvaMed has engaged in discussions with the offices of Representatives Markey and Rogers about the device industry's concerns (outlined below) and we are hopeful we can reach an acceptable agreement.

Because FDA has indicated it already has authority to require postmarket surveillance for any device at any time, including at the time of approval or clearance, we believe the language giving FDA authority to require postmarket surveillance as a condition of approval or condition of clearance is unnecessary. Importantly, the language as currently drafted has the unintended consequence of adversely impacting the availability of safe and effective medical devices for the broader population.

We are also concerned that the postmarket surveillance database duplicates an effort that FDA has already undertaken—to create a database of all postmarket surveillance device studies. There is no need to legislate the creation and maintenance of a new database—a costly and expensive proposition.

In addition, as we attack the problem of limited availability of pediatric devices for children, we need to address the root causes—lack of knowledge of pediatric needs and lack of incentives. The market for pediatric uses is often very limited, while the cost of development and regulatory clearance or approval can be com-

parable to the adult market. Unlike drugs, the kinds of incentives that exist in the Best Pharmaceuticals for Children Act are not available to the device industry. Creating incentives such as improvement in the pediatric HDE program, establishing a new compassionate use pediatric device provision, using existing regulatory mechanisms to facilitate device clearance and approval without reduced safety and efficacy standards for children, or creating tax credits or grant programs for companies developing pediatric devices could improve pediatric device access.

We thank Congressmen Markey and Rogers for their leadership on pediatric issues and look forward to working with them and members of the Subcommittee and the Full Committee to resolve the important, outstanding issues on this legislation.

CLINICAL TRIAL REGISTRY AND RESULTS DATABASES

AdvaMed supports patient and doctor access to important information about the health benefits and risks of medical devices. The current language, however, would harm device innovation without any benefit to patients. We support the Senate language which requires disclosure of all clinical trial information once a device is actually available to patients.

In the competitive device environment, protecting proprietary technology is especially important because patents provide little protection for devices. Engineering or design changes can readily negate device patents whereas for drugs, entire molecules are patented, frequently before the first trial begins. As a result, disclosure of the existence of an Investigational Device Exemption (IDE) or related data in a registry could unfairly reveal important proprietary information to competitors who could speed competing devices into trials, obtain FDA clearance or approval and take advantage of the significant benefits associated with being first-to-market. When there is no FDA-approved product, information related to the device design and to the design of the trial and its endpoints is the only intellectual property a company may have.

Such disclosures could have the unintended consequence of eliminating many small device companies from the marketplace. Small companies account for the vast majority of device innovation and contribute greatly to maintaining strong price competitiveness across the industry.

DIFFERENCES BETWEEN DRUGS AND DEVICES

We encourage the House to consider including a recognition of the differences between drug and device trials in their database requirements. The Senate bill, for example, requires early registration of device clinical trials but protects sensitive intellectual property and trade secrets until the device is cleared or approved. In addition, S. 1082 recognizes that the vast majority of device companies are small and allows a link to the FDA-required PMA Summary of Safety and Effectiveness (SSE) or the 510(k) Summary to satisfy the bill's results requirements. More than 70 percent of AdvaMed's members have less than 50 employees and fewer than $30 million in sales annually. They will be unable to manage the extremely burdensome requirements of this legislation. The SSE and 510(k) Summary include a detailed summary of information on the clinical trials that supported the PMA or 510(k) application including information on any adverse events during the trial.

Finally, the discussion draft includes a requirement that any agreement that prohibits an investigator from discussing or publishing the results of a trial must be included in the clinical trials registry and results databases. The provision indicates a fundamental misunderstanding of the current nature of most device clinical trials which are multi-center trials (multiple sites and investigators conduct the trial). While device trials are much smaller than drug trials, they typically require multiple sites to assist with recruitment. FDA may also require multi-center trials in order to see experience over several sites. It is standard procedure to require investigators to withhold discussing or publishing the results of a trial at their particular site until the data from all of the sites has been aggregated. Discussion or publication of information from one site could provide false or misleading information about the trial and could introduce bias (positive or negative) into the study that could jeopardize the integrity of the trial. Further, premature discussion or publication of one site's trial information could jeopardize publication of the aggregate data later in a peer-reviewed journal. Most medical journals refuse to publish information that has previously been released. Thus, there is a legitimate need for restrictions on discussion or publication until the data has been aggregated. Although there are rational and legitimate reasons to restrict individual investigators from premature release of information, the legislative requirement to reveal these restrictions will unfairly paint sponsors as bad actors.

To ensure continued medical device innovation for patients, AdvaMed recommends that the House legislation:

• Delay disclosure of device clinical trial registration information until the device is cleared or approved.
• Allow device companies to satisfy results requirements via a link to the PMA SSE or 510(k) Summary.
• Eliminate the faulty provision requiring disclosure of agreements that prohibit investigators from prematurely discussing or publishing clinical trial results.

AVAILABILITY OF ADVISORY COMMITTEE MEMBERS WITH APPROPRIATE EXPERTISE

The House bill prohibits an advisory committee member from voting on a matter if that member, or an immediate family member, has a financial interest that could be affected by the committee's advice to FDA. The agency may grant a waiver of this prohibition if a waiver is necessary to afford the advisory committee essential expertise; however, only one waiver may be granted per committee meeting. AdvaMed is extremely concerned that the limitation of one waiver per committee meeting could prevent FDA from convening a panel of experts with the appropriate expertise to address the matter at hand. Because the waivers will be publicly disclosed, thus making the committee process transparent, we do not believe there is any harm in granting more than one waiver to highly qualified experts who bring unique expertise to the committee meeting. Advisory committees have been challenging to form because of the difficulty in recruiting the persons most expert in a type of device. We believe the House's one waiver limitation undermines other elements of this legislation which require FDA to conduct outreach and recruit potential members to advisory committees, including those who have waivable conflicts.

IOM REPORT ON PREMARKET NOTIFICATIONS

The MDUFMA discussion draft requires an Institute of Medicine (IOM) "study on the appropriate use" of the 510(k) process "to clear medical devices as safe and effective." Although commonly referred to as a "clearance" system, the premarket notification system actually is a classification system which regulates classes of devices according to their risk profile. Congress developed the premarket notification process to mirror the incremental innovation process that occurs in medical technology and where appropriate to help expedite incremental improvements in devices through the regulatory process. Upon submission of a premarket notification, FDA determines whether the device is "substantially equivalent" to a predicate device. To be substantially equivalent, the device must have the same intended use and the same technological characteristics as the predicate, or if it has different technological characteristics, there must be information submitted to FDA that demonstrates that the device is as safe and effective as a legally marketed device and does not raise different types of safety or effectiveness questions from the predicate device. Many 510(k) devices or their predicates have been on the market more than 30 years (i.e., prior to the Medical Device Amendments of 1976) and their benefits and risks are well-known and well-qualified.

Congress has fine-tuned the 510(k) process over its 30-year history to ensure that FDA has the necessary tools and can devote appropriate resources to devices as needed, including those which present a higher risk. Importantly, The Safe Medical Devices Act of 1990 (SMDA) strengthened the 510(k) premarket notification process by requiring substantial equivalence decisions to be made to currently marketed technology—not to technology that is no longer on the market. This has the effect of ensuring that FDA's substantial equivalence decisions are made to the most advanced technology available. SMDA also required that premarket notification submissions include detailed information concerning potential adverse health effects. Finally, SMDA gave FDA authority to impose a wide range of special controls including performance standards, postmarket surveillance, the submission of clinical data, the development of patient registries, and any other appropriate action needed to provide a reasonable assurance of the safety and effectiveness of a device.

While AdvaMed supports any independent analysis of the premarket notification system to ensure the system is operating to its full potential, because of the complexity of device regulation, any such analysis must be fully informed and include the perspectives of all potentially affected parties. It is important that any IOM review of the 510(k) process include a device representative. AdvaMed would want to ensure that any review of the 510(k) process thoroughly consider the views of its members.

In summary, AdvaMed strongly supports the reauthorization of MDUFMA. However, we have serious concerns with the draft legislation as proposed, and we ask

that you consider the changes we have requested to ensure that the final draft accomplishes the goal of ensuring that Americans have access to safe and effective medical technology as soon as possible. We thank the Subcommittee again for its interest in these important regulatory issues. We look forward to working with Congress and the FDA on this legislation.

Mr. PALLONE. Thank you. Dr. Zuckerman.

STATEMENT OF DIANA ZUCKERMAN, PRESIDENT, NATIONAL RESEARCH CENTER FOR WOMEN AND FAMILIES

Mrs. ZUCKERMAN. Thank you for the opportunity to testify today. I am Dr. Diana Zuckerman, president of the National Research Center for Women and Families, an independent think tank that analyzes and evaluate health programs and policies. I was trained as an epidemiologist at Yale Medical School and I have worked on health policy issues for more than 20 years.

Every American relies on medical devices and more than 5,000 medical devices were cleared or approved by the FDA last year. Ninety-eight percent were cleared through a quick and easy 510(k) process that usually does not require clinical trials to prove that the products are safe and effective. So I am going to start by focusing on that 510(k) process and the relevance to your legislation.

We strongly support provisions in your discussion draft that would address concerns with the 510(k) process. We applaud your decision to keep the user fees for each 510(k) application at the current level, and your decision not to speed up the already speedy review process for the 510(k). Keeping the status quo will put less strain on CDRH, since almost all the devices are reviewed that way. You have asked for an IOM report on the 510(k) process and we think that is a great idea and I have some slides to show you why.

[Slide]

Unlike drugs, most medical devices do not need to be proven safe and effective, and under the 510(k) process, devices are cleared if they are deemed substantially equivalent to other devices that were on the market prior to 1976. Originally, the term substantially equivalent was expected to mean that they were very similar, but that definition has changed over the years and today, as long as the products are used for the same purpose, they don't need to be the same shape, made from the same materials, use the same mechanism of action, or be equivalent in any other substantial way. And so if you look at this first slide, steak and milk are more substantially equivalent than the FDA would require. Both are food; both are from cows. But let us look at some medical device examples instead. Next slide.

[Slide]

Here is a jaw implant made by Vitek, the one on the left. It was cleared as substantially equivalent to silicone sheeting, which you see on the right. You can see they are completely different. They look different and they are even made from completely different materials. The Vitek implants were made with Teflon and clinical trials were not required and so nobody knew that the Teflon would flake off inside people's jaws and that that would cause the jaw bone to degenerate, to basically disintegrate. Patients ended up unable to speak or to eat and some with holes in their skull with their

brain no longer protected. Vitek jaw implants were recalled, but they could not be safely removed from all patients. Next slide, please.

[Slide]

Last month a contact lens solution was recalled because it causes serious eye infections that can cause blindness. That is completely different from the contact lens solution that was recalled a year ago, a completely different solution which also caused a different eye infection which could also cause blindness. Both of these contact lens solutions were approved as substantially equivalent to older, safer contact lens solutions, and you can see that those eye infections caused by those new solutions are really terribly serious. Slide 3, please.

[Slide]

Bladder slings are used to treat stress incontinence in women. The slings made by Boston Scientific called ProteGen were made from a different material than slings that looked the same. You can see these are diagrams are identical. The slings look the same but they are made of a different material. So the ProteGen was made out of a new synthetic material, whereas the old slings are made of Gor-Tex or other materials that had been found to be safe. The ProteGen slings were recalled because they caused more infections, they caused vaginal erosion and other serious problems. The last slide, please.

[Slide]

Yes, apples and oranges are both fruit, they are both round and they are both good for you, but they have different advantages and they are not substantially equivalent. That is why we have the expression apples and oranges. They are different. And the FDA needs to define substantially equivalent to make sure that the products that they are reviewing really are the same. If they are not, clinical trials are needed.

So for all its faults and despite Vioxx and Avandia and other lapses, the FDA approval process for prescription drugs is really much more cautious and rigorous than the device approval process. And in speaking with physicians, scientists and consumer advocates, we have developed several suggested changes in the 510(k) process, which is in my written testimony. From a policy point of view, when new devices are approved through the 510(k) process, if there are no studies published, they are not going to be covered by the Center for Medicare and Medicaid Services and they are not covered by insurance. So all the rush to get them to market doesn't really help patients, if they are not reimbursed through health insurance.

So when you ask the IOM or the GAO to examine the 510(k) process, which is going to take at least a year or two, I urge you to consider a temporary moratorium on approving implanted medical devices that have not been carefully evaluated with clinical trials. And I just want to finish by saying that the FDA has made it clear that post-market analysis is very important and it is especially important for medical devices because so many are cleared without clinical trials. We think registries with unique identifying numbers on products are very helpful and important, and we think the adverse reporting system needs to be improved. So we are very

pleased that your discussion draft includes additional funding and we urge you to specify how that funding will be spent.

Finally, I just want to say a couple of words about direct-to-consumer advertising on medical devices.

Mr. PALLONE. OK. Quickly, though, because you are almost at 2 minutes.

Ms. ZUCKERMAN. I promise. Sorry.

Mr. PALLONE. Over, I mean.

Ms. ZUCKERMAN. OK. Medical devices are also advertised through direct-to-consumer advertising and any restrictions for DTC ads for drugs should also be considered for devices. And we also support your decision not to expand the third-party inspections. Since the current program has not worked very well, we think it would be foolish to expand it before you can figure out why it isn't working better and what needs to be done. Thank you very much.

[The prepared statement of Ms. Zuckerman follows:]

Statement of Diana Zuckerman, Ph.D.
President, National Research Center for Women & Families

Before the Subcommittee on Health
House Subcommittee on Energy and Commerce
June 12, 2007

Thank you for the opportunity to testify about the Subcommittee's discussion draft FDA legislation. I am Dr. Diana Zuckerman, president of the National Research Center for Women & Families, an independent think tank that analyzes and evaluates a wide range of health programs, policies, and agencies, including the FDA.

I am trained as an epidemiologist at Yale Medical School and for more than a dozen years I worked in Congress, the U.S. Department of Health and Human Services, and the White House, determining which health policies were working and which ones were not.

Our center is an active member of the Patient and Consumer Coalition, comprised of nonprofit organizations representing patients, consumers, public health researchers and advocates, and scientists. The Coalition is working to strengthen the FDA and to ensure that FDA approval once again represents the gold standard of safe and effective medical products. Our Center is also an active member of the FDA Alliance, which is a coalition of pharmaceutical companies, medical device companies, former FDA officials, and consumer and patient organizations that work together to support increased resources for the FDA. I am proud to serve on their Board of Directors.

In my testimony, I am speaking on behalf of the National Research Center for Women & Families, not on behalf of other organizations we work with. I will start my testimony by focusing on medical devices and MDUFA, but will also include a brief analysis of PDUFA and other issues that you are considering in your legislation.

Every American relies on medical devices -- whether they use band-aids, contact lenses, or pacemakers. Baby boomers increasingly rely on implanted medical devices, whether hips, heart valves, or wrinkle fillers.

More than 5,000 medical devices were approved by the FDA last year. Almost all (98%) were cleared through a "quick and easy" process that usually does not require clinical trials to prove that these medical devices are safe or effective. As a result, some of these devices are neither safe nor effective.

Are medical devices "proven safe and effective"? Not usually.

The American public is very concerned about the FDA drug approval process, wondering how Vioxx, Avandia, and so many other drugs can be prescribed by physicians who are not given accurate information about the risks, and then sold to millions of patients who are unable to make informed decisions about their own medical care. For all its faults, however, the FDA approval process for prescription drugs is much more rigorous than the device approval process.

There are two ways that the Center for Devices and Radiological Health (CDRH) approves medical devices, and neither has the same criteria – to prove that the product is safe and effective – that the drug approval process requires. In a book published this year, FDA officials state, "The FDA is responsible for ensuring that there is reasonable assurance that a medical device will be useful while not posing unacceptable risks to patients." That standard is certainly more vague and less stringent than the standard for prescription drugs, and yet medical devices are just as important for saving lives and protecting the quality of people's lives.

The statement is an accurate reflection of the FDA approval process for medical devices. In fact, most medical devices – approximately 98% -- are allowed to be sold after a review that does not usually require any clinical trials. Device companies don't need to prove that their products are "safe and effective" – they only need to prove that they are "substantially equivalent" to a product that was on the market before 1976. This much less rigorous process is known as the 510(k) process.

The 510(k) process was intended to be a temporary alternative to a full review when the FDA first was given the authority to regulate medical devices in 1976. This authority was the result of thousands of women being harmed by the Dalkon Shield IUD (intra-uterine device), which was found to cause serious infections, permanent infertility, and even death.

When the FDA started regulating medical devices, there were thousands of different devices on the market that had never been proven safe or effective. Most were "grandfathered" -- allowed to stay on the market -- with the FDA requiring some companies to conduct and submit safety studies for the first time. At the same time, to be fair to companies that wanted to sell medical devices that were similar to untested devices that were already on the market, section 510(k) of the Food, Drug, and Cosmetics Act gave the FDA the authority to "clear a product for market" if it was deemed "substantially equivalent" to medical devices already being sold.

We think that decision made sense. If logic had prevailed, however, FDA would have eliminated or at least drastically reduced their use of the 510(k) process in the three decades since 1976. Instead, the process was continued, with the rationale that device manufacturers are constantly improving their products and that it would stifle innovation to require each small change to be reviewed by the FDA in the more careful premarket approval (PMA) process. The assumption has been that a medical device that has been modified very slightly does not need to be tested as carefully as a new product.

Unfortunately, over time the definition of "substantially equivalent" was changed to include almost any product for the same medical condition. The FDA is now using the 510k process for 98% of the medical devices that they review. **As a result, new products, using new materials, or a new mechanism, made by a different manufacturer, are being reviewed as if they were a mere tinkering improvement over previously sold products. In fact, it doesn't even matter if the previously sold product was subsequently found to be unsafe or ineffective and is no longer for sale.** There are medical devices on the market today that were approved as "substantially equivalent" to products that were subsequently recalled for safety reasons.

Why Clinical Trials are Needed

Even small changes to a medical device can affect safety, and can be very dangerous. For example, when Bausch & Lomb added MoistureLoc to their contact lens solution, the new product was approved through the 510(k) process. No clinical trials were required. The result: severe eye infections causing blindness and the need for corneal transplant surgery.

Although the standard of "substantially equivalent" for devices sounds almost like the standard for a generic drug, the reality is completely different. Many medical devices approved by the FDA through the 510(k) process are not like any medical devices already on the market, and are instead made of different materials, used for different purposes, use a different technology, or are otherwise "new and different" rather than slightly improved.

A Few Examples of 510(k) Device Disasters

TMJ Implants: Vitek jaw implants were cleared as "substantially equivalent" to silicone sheeting, which was made from a different material and was not developed for use in a joint. The Teflon from the Vitek implants broke off into particles that caused bone degeneration in the jaw joint and skull. Some patients can no longer eat, others have holes in their skulls.

Bladder Slings: Boston Scientific won approval for a ProteGen bladder sling to treat stress incontinence. The sling, made of a new synthetic material coated with collagen, caused vaginal erosion.

Pacemakers and Defibrillators: Frequently reviewed with the 510(k) process, tens of thousands of pacemakers and defibrillators have been recalled in recent years. When these products are defective, patients can die.

ReNu with MoistureLoc Contact Lens Solution: Bausch & Lomb's contact lens solution was found to be an excellent breeding ground for a fungus that caused severe eye infections. One-third of consumers who developed the eye infections needed to have their eyesight restored with corneal transplant surgery. The product was recalled in May 2006.

Complete MoisturePlus Contact Lens Solution: Advanced Medical Optics' contact lens cleaning and storing solution was found to not protect against a different bacteria that can cause severe eye infections. It was recalled in May 2007.

Shelhigh heart valves and other implants: In April 2007, the FDA seized all implantable medical devices from Shelhigh, Inc., after finding deficiencies in manufacturing. The devices are used in open heart surgery in adults, children and infants, and to repair soft tissue during neurosurgery and abdominal, pelvic and thoracic surgery. "Critically ill patients and pediatric patients may be at greatest risk," according to the FDA.

How does this affect the practice of medicine? According to Dr. Donald Ostergard, past president of the American Urogynocologic Society, many medical devices used to treat incontinence and other urological conditions were not required to conduct clinical trials before being sold. As a result, surgeons considering the use of a new device must rely on colleagues' anecdotal experience or promotional information from the manufacturer. He points out that some have caused serious problems that were not identified until the device had been used on hundreds or even thousands of women. As a result, patients who started out with a minor health problem can end up with many surgeries and with permanent and debilitating health problems.

Part of the problem is the very loose definition of "substantial equivalence." As long as a product is used for the same general purpose – such as the treatment of depression or cancer – and if its risk to benefit ratio seems to be similar, a product can be approved as "substantially equivalent." Not to be glib, but this would be like saying that cheese is substantially equivalent to peanuts or bread because all three are food that provide nutrition, and each has risks and benefits for the general population. But, if you are allergic to peanuts, or sensitive to milk products, you know that there is a world of difference regarding how those foods will affect you, and the percentage of people who can be harmed by them. They are not interchangeable.

In addition to other safety concerns about the 510(k) process, current law permits manufacturers to hire a third party to review their devices, instead of the FDA. The goal is to speed up the review process and reduce the FDA workload. However, according to the FDA, the program has not reduced the FDA workload because of the use of FDA staff to administer the program. The benefit to device manufacturers is modest since the companies must pay the third parties and the review time is reduced by an average of less than two weeks.

Why are 98% of Medical Devices Reviewed Through the 510(k) Process?

CDRH has a modest budget and fewer resources than the Center for Drug Evaluation and Research (CDER). And yet, they have a greater workload in terms of number of devices submitted to them for review every year. It is not surprising that the FDA has increasingly relied on the less labor intensive 510(k) process to review the thousands of products submitted for review every year.

Under the current law, 80% of 510(k) reviews are completed within 90 days. This is a very short turnaround time, making it difficult for the more complicated applications to receive careful evaluations.

In speaking with physicians, scientists, and consumer advocates, we have developed several suggested changes in the 510(k) review. The goal is to increase useful information for physicians and improve safeguards for patients. These changes, supported by most members of the Patient and Consumer Coalition, include:

- Excluding implanted medical devices from the 510(k) process;
- Requiring clinical trials for all medical devices that could harm patients and consumers; and
- The FDA needs to establish an appropriate definition of "substantial equivalence." They should revert to the original intent of the 510(k) process: the review of products that are substantially equivalent in terms of intended treatment, form, what they are made of, mechanism, and function.

We know that device manufacturers believe that the 510(k) process is safe enough and necessary to get products to patients more quickly. From a policy point of view, however, many medical devices cleared for sale by the FDA under the 510(k) process are **not reimbursable under Medicare or Medicaid, or by private insurance companies.** The Center for Medicare and Medicaid Services (CMS) and insurance companies have higher standards for reimbursement than the FDA has for device approval. Although thousands of medical devices are cleared for market by the FDA through the 510(k) process every year, many Americans will not have access to all those products because insurance companies require published research to prove that the products are safe and effective. For many important products, the patient will not benefit at all until those studies are done.

If medical devices are not reimbursable until peer reviewed studies are published, then the 510(k) process is NOT getting many new, innovative products out to patients more quickly. Research will still need to be conducted. Wouldn't it be better to make sure that the studies are evaluated by the FDA through the PMA process, to make sure that the analyses are not manipulated to minimize the risks?

We strongly support the Committee's plan to require a study of the 510(k) process. Either the IOM or GAO could do a credible study and report, and we urge you to determine which can do the best job in the next 12-18 months.

The "Full Review" Premarket Approval Process

The more rigorous approval process, which is similar to the process for prescription drugs, is called the premarket approval (PMA) process. Drug companies and device companies must conduct clinical trials and other tests to determine that their products work well and are safe. However, the drug approval process requires that the products be "proven safe and effective." The approval process for medical devices has a lower standard: the products must provide merely a "reasonably assurance of safety and effectiveness."

That rather vague definition is not an appropriate standard. In our Center's review of thousands of pages of FDA advisory committee transcripts, we found how dangerous this vague definition can be. For example, at an FDA advisory panel meeting on the Kremer LASIK device, a physician explained that she recommended approval "because I did not see from the data that this was totally unsafe or totally ineffective." At a different FDA advisory panel meeting for a device to treat Alzheimer's Disease, a neurosurgeon recommended approval after saying, "Only time will tell whether or not this will pan out to be helpful." The FDA went along with advisory panel recommendations for approval almost every time. With standards like these, patients and their families will waste billions of dollars on

products that are not proven safe and effective, do not benefit them, and that replace products that might have helped save their lives or improve the quality of their lives.

There is no logical reason why the standard for the PMA should be any different than the standard for prescription drugs. All medical products should be required to be proven safe and effective. That does not mean that the product has no risks, but it should mean that the benefits outweigh the risks for the people who will be using the product.

Post-market Studies, Surveillance, and Advertising

Since so many medical devices are approved through the 510(k) process, and the rest are approved on the basis of the vague criteria of "reasonably safety and effectiveness" it would make sense for CDRH to devote a great deal of resources to post-market surveillance. In fact, the CDRH often requires post-market studies be conducted, but they do not monitor those studies to make sure that they are done appropriately.

For example, in 2000 CDRH approved saline breast implants on the condition that 10-year post-market studies be conducted. Because of the enormous media attention and controversy, the CDRH required the implant makers to present their 5-year data at a public meeting in 2003. At the meeting, it was shown that one of the companies, Mentor Corporation, had lost track of 95% of their augmentation patients after 5 years.

Any epidemiologist will tell you that when you lose track of 95% of your patients, your study does not provide useful safety information. The FDA criticized the company, and encouraged them to re-contact more of the patients in their study. However, even with more extensive follow-up, more than two-thirds of the patients were missing from the post-market study at the six-year follow-up. And yet, the company continued to sell their product with no penalties. They even came back for approval of their more controversial silicone gel breast implants two years later, and those implants were approved on the basis of the company's promise to study those women for 10 years. In other words, they made the same promise that they had previously broken, and the FDA approved their product anyway.

In a recent book, the director of CDRH wrote that "the premarket evaluation program alone cannot assure continued safety and effectiveness of marketed devices" and explained the need for post-market surveillance to determine the risks after a product is approved and widely used. Thus far, those efforts have been under-funded and ineffective. Registries for implanted medical devices and improvements to the adverse reporting systems would provide important information to doctors and patients about devices already on the market. The Energy & Commerce Discussion Draft of MDUFA authorizes additional funding that would make post-market surveillance possible, but does not require specific post-market surveillance activities.

Under current law, if an implanted device is recalled, it is unlikely that the men, women, or children who have that device in their bodies will be notified. Doctors and medical centers will be notified, but they may not be able to notify all – or even most – of their patients. Registries for implanted devices, using unique identifying numbers, are needed to help

ensure that patients will be notified as quickly as possible if there is a defective implant inside their body.

MDUFA does not include any user fees for the review of direct-to-consumer (DTC) advertising, which has been increasing greatly for medical devices. For example, in the spring of 2007, Allergan Corporation has extensive DTC ad campaigns for three medical devices: gastric lap bands (which are surgically inserted for weight loss), Botox, and Juvederm; the latter two devices reduce wrinkles, and are injected by a physician. Allergan is currently preparing an ad campaign for silicone gel breast implants. The ads on their Web site and on TV feature enthusiastic patient testimonials with no meaningful risk information. According to the Allergan Web site, the patients receive free treatment, worth thousands of dollars, as compensation for their testimonials.

Speed and Safety

The MDUFA Discussion Draft would not speed up the 510(k) process, which is already very fast, reviewing 80% of the products within 90 days. That is a wise decision. It is important that the legislation focuses on decreasing the cost of user fees for the smaller companies, but does not reduce the already very inexpensive user fees for 510(k) reviews.

The decrease in funding for the PMA process seems reasonable, as long as the process is not required to speed up. The total funding, and the increase in appropriations authorized, would help ease the stress on CDRH staffing levels and improve their ability to conduct careful reviews.

Third Party Inspections

Rather than FDA conducting inspections of manufacturing facilities, device companies can directly pay a third party to do the inspection, and can negotiate the price of the inspection. The current law includes very modest restrictions on third party inspections of Class II and Class III medical devices, which are the most stringently regulated devices. The current law allows two consecutive third-party inspections, after which the FDA must conduct the next inspection (unless the FDA issues a waiver).

The MDUFA discussion draft wisely does not expand this program. Critics have compared third party inspections to allowing parents to select and pay a third party to determine school grades for students, or allowing employees to hire a third party to make salary and promotion decisions. According to 2007 FDA testimony, the agency has spent millions of dollars on this program, but it has very rarely been used. We urge the Committee to ask the GAO or IOM to evaluate whether this program is workable and cost-effective, or whether the funds should instead be used to hire more FDA inspectors.

Progress on PDUFA and Safety Issues for Drugs, Devices, and Biologics

The FDA discussion draft legislation includes many important provisions that will greatly improve the safety of drugs and potentially the safety of all medical products.

We strongly support the proposed addition of **$225 million** over five years in new safety money, and urge Congress to make sure that funding is used to improve resources to conduct post-market surveillance and modernize the FDA's computer systems, including **software for reporting and analyzing adverse reactions for drugs and devices**. We also strongly support the provision that **would include patient and consumer organization representatives in the negotiations for any PDUFA renewal and MDUFA renewal.** The patient and consumer organizations represented should be full partners at the negotiations, and should not have financial ties to pharmaceutical or medical device companies.

The proposed legislation builds on the best **REMS provisions** in the Waxman-Markey bill (HR 1561), giving the FDA the authority it needs.

For drugs and medical devices, it is important that there be required registration of all Phase II thru IV trials. We agree with the discussion draft provision that the results of all these studies should be made publicly available, and that should apply to studies on medical devices as well as drugs.

In **Section 5**, the discussion draft includes the Senate bill's section 201, which is based on a suggestion by former FDA Commissioner Dr. Mark McClellan and introduced in a bill by Senators Gregg, Burr, and Coburn (S. 1024). In combination with REMS, these **databases** from Medicare and elsewhere are very important because they can be used to detect short- and long-term safety problems in **drugs and devices.**

We support the discussion bill's recognition that **nothing in these FDA bills pre-empts state tort laws.**

Additional Suggestions for Devices and Drugs

As a member of the Patient and Consumer Coalition, our Center strongly supports several recommendations to strengthen provisions in your discussion draft of PDUFA and other FDA legislation.

Although the conflicts of interest" provision is a clear improvement over the Senate bill, we believe that **conflicts of interest should be eliminated in FDA advisory committees for drugs and devices,** by excluding any members with stock, stock options, or other financial ties to companies that have stakes in the topic under discussion. The discussion draft includes a good provision on conflicts of interest, but it is essential that "conflicts of interest" be defined in the law as a financial relationship within the last 36 months. Otherwise, FDA advisory committees could include members who received million dollar honoraria from the company whose product is under review just 13 months prior to the committee meeting. And, since stock and stock options are so strongly affected by FDA decisions, either should always be unacceptable for advisory committee members.

Better consumer protections regarding DTC advertising is needed. The discussion draft section on DTC advertising is a good start, but needs to be strengthened by making pre-clearance of all DTC advertising for drugs and devices mandatory rather than

voluntary. An effective system of civil monetary penalties is also needed, and those must be substantial to be an effective deterrent.

Strong whistle-blower protection provisions are needed, as well as a provision clarifying the **right of FDA officers and employees to publish scientific articles**, with proper disclaimers. The right to publish could have meant earlier warnings about the risks of Vioxx, Avandia, Actos, and other blockbuster drugs and devices, saving the lives and improving the quality of life of many Americans.

In addition to the provisions in the discussion drafts on making data available, we strongly urge that you consider the Senate provisions making **FDA reviews, evaluations, and approval documents promptly available to the public**, including dissents and disagreements. In addition, the FDA should be required to **publish observational study results**, in addition to clinical trial results.

We support legislation by Representatives Tierney, Emerson, and Stupak that would create a separate **Center for Post-market Evaluation and Research** with real clout within the agency, but strongly urge that the Center include devices as well as drugs and biologics.

In conclusion, thank you for the opportunity to testify and share our views about the discussion drafts. You have made important progress, and we appreciate your consideration of provisions that would strengthen this legislation to help ensure that safe and effective medical products are available to all Americans.

Mr. PALLONE. Thank you. Mr. Walker.

STATEMENT OF STEVE WALKER, CO-FOUNDER AND CHIEF ADVISOR, ABIGAIL ALLIANCE FOR BETTER ACCESS TO DEVELOPMENTAL DRUGS

Mr. WALKER. Mr. Chairman, Congressman Deal, members of the committee, we at the Abigail Alliance wish to express our thanks for this hearing and for inviting us to testify. I am Steven Walker, co-founder and chief advisor to the Abigail Alliance. I receive no compensation of my efforts as an advocate and I pay my own expenses.

The Abigail Alliance for Better Access to Developmental Drugs is a nonprofit, nonpartisan patient advocacy organization dedicated to serving the needs of people suffering from serious and life-threatening diseases.

Based on our firsthand experience with the harsh regulatory realities faced by patients with life-threatening diseases, we have proposed a solution called Tier 1 Initial Approval to ease the regulatory barriers our constituents face, while simultaneously protecting the clinical trial system. Tier 1 was submitted to the FDA in a citizens petition 4 years ago yesterday and we are still waiting for a response, and I wonder if I could have the 2-week thing that Congresswoman DeGette got on that?

Last year a bill called Access Act passed based on our tier 1 proposal. It was introduced in both houses of Congress and it is going to be reintroduced this year and we strongly urge Congress to pass the bill. Incidentally, legislation to address the needs of our constituents should have been included in the discussion draft today.

In July 2003, we filed a suit against the FDA in Federal court, claiming that the FDA's denial of access to promising investigational drugs for patients with no other option but death from their disease, violates their constitutional rights of due process and privacy. Last year a three-judge panel of the DC Federal Court of Appeals agreed, but the FDA moved for a rehearing by the full appeals court and almost 4 years after filing the suit, we are still awaiting a trial on the merits of the claim. Over those 4 years, 2.2 million Americans died from cancer alone. This is not just a regulatory policy issue. It is a civil rights issue. Now I am going to turn to a few of your discussion drafts.

The Abigail Alliance has long sought readily available and more complete listings of clinical trials and access programs for investigational drugs, and we support the proposed clinical trials registry in the discussion draft. We also support in concept the idea of making the results of clinical trials public. But we think the clinical trials results database as proposed in the discussion draft has all the earmarks of a major regulatory misstep. The evidence for this can be found in the recent flap over Avandia. The publication of scientifically-weak analysis results in the New England Journal of Medicine was a statistical drive-by hit on the integrity of our regulatory system. If the results database is enacted as proposed, the FDA will become the regular target for poorly-constructed statistical hand grenades and spend far too much of its time trying to clean up the mess after each one explodes in sensational fashion in the media. We ask that the committee schedule future hearings

to receive additional input on how to make trial results public, while at the same time preserving the integrity of our regulatory system.

On advisory panel conflicts of interest, we think you are missing the point. We think you are putting the cart before the horse. The Federal Advisory Committee Act prohibits inappropriate influence by the appointing authority of its advisory committees. But FDA review office directors are empowered to manipulate the ideological makeup of their advisory committees, and potentially use that power to pursue the outcome they want regarding policy matters and votes on specific drugs. We believe that this has, in fact, happened with some cancer drugs. Congress should start by looking at the FDA's process for selecting advisory committee members at the detail level and then take up the conflict of interest measures.

On REMS, we oppose the proposal to require mandatory Risk Evaluation and Mitigation Strategies, or REMS, because they are mandatory, making them yet another one-size-fits-all solution that won't work. The FDA already has and uses the authority to impose what they call risk management plans, or RiskMAPs, on drugs at the time of approval. RiskMAPs has so far been a mixed bag of safety controls burdened with unnecessary approval delays and proscribing restrictions, coupled with requirements for highly unethical post-approval clinical trials. Remember, people are put into these clinical trials. They are not just exercises in data collection. RiskMAPs also have resulted in major intrusions by the FDA into the practice of medicine. Mandatory REMS, even though proposed as being flexible, are likely to evolve quickly into an over-applied defensive mechanism for FDA, instead of its intended use of being a rational, sober post-marketing tool. We need post-market monitoring of drugs, but we do not need anymore one-size-fits-all solutions. We suggest that the flexible model for what must be included in the REMS be used to replace the current RiskMAP model, but that the need for a REMS be determined on a case-by-case basis. And believe me, I find it odd that I am in agreement with the FDA. I am usually not.

The Reagan-Udall Institute for Applied Medical Research is a very good idea that could be made even better. The goal is regulatory modernization and that can only come through real change in the way the FDA does its job. Consequently, the institute should be moved inside the FDA and given line authority to issue new policies and guidance and to initiate rulemaking on its own.

I have some closing comments. This entire debate regarding FDA reform has its roots in a decades-old feud raging within the FDA and the medical research community, between two groups of statisticians: those who believe the forward-looking trials used for pre-approval testing, and those who support the backward-looking trials who try to find drug safety needles in haystacks. Neither statistical camp should win this feud. Patients should win. And for that to happen, we need to move away from the rigid, often unethical statistical approaches we have now and move toward real science. We need to remember that the FDA's mission is not to control and punish the drug companies, but rather to protect and promote the public health, and it is on the promote side where we will find better treatments and cures for diseases like cancer.

I would like to close with an important fact. Every investigational drug for which the Abigail Alliance has sought early access was eventually approved by the FDA. We knew that patients would be better off if they could get the drug than if they could not, usually years before the FDA enacted to make those drugs available. If the FDA was less a barrier to progress, millions more would have gained access to that progress over the last 7 years. Thank you.

[The prepared statement of Mr. Walker follows:]

Written Testimony of Steven Walker
(with references and attachments)
Abigail Alliance for Better Access to Developmental Drugs

Discussion Drafts of Legislation on PDUFA, MDUFMA, Drug Safety, Pediatric Safety, Pediatric Incentive, and Pediatric Devices

Energy and Commerce Committee
Subcommittee on Health
June 12, 2007

Mr. Chairman, Congressman Deal and members of the Committee, we at the Abigail Alliance wish to express our thanks for this hearing, and for inviting us to testify.

My name is Steven Walker, Co-Founder and Chief Advisor to the Abigail Alliance. I receive no compensation for my efforts as an advocate, and I pay my own expenses. *(See Attachment A, S.O.S. to the FDA, editorial in the Wall Street Journal, August 26, 2003, by Steven Walker)*

The Abigail Alliance for Better Access to Developmental Drugs is a non-profit, non-partisan patient advocacy organization dedicated to serving the needs of people suffering from serious and life-threatening diseases.

Based on our first-hand experience with the harsh regulatory realities faced by patients with life-threatening diseases, we have proposed a solution called Tier 1 initial Approval to ease the regulatory barriers our constituents face, while simultaneously protecting the clinical trials system. Tier 1 was submitted to the FDA in a Citizens Petition four years

ago, yesterday. We are still waiting for a response. *(Our Citizens Petition and related information can be found at www.abigail-alliance.org.)*

Last year a bill called the Access Act based on our Tier 1 proposal was introduced in both houses of Congress. It is going to be reintroduced this year and we strongly urge Congress to pass the bill. Incidentally, legislation to address the needs of our constituents should have been included in the discussion drafts today. *(The legislation as introduced in the Senate in the 109th Congress is posted at www.abigail-alliance.org. The house version was identical.)*

In July 2003, we filed a suit against the FDA in federal court, claiming that the FDA's denial of access to promising investigational drugs for patients with no other option but death from their disease, violates their Constitutional rights of due process and privacy. Last year, a three judge panel of the DC Federal Court of Appeals agreed, but the FDA moved for rehearing by the full appeals court, and almost four years after filing the suit, we are still awaiting a trial on the merits of our claim. *(The original lawsuit is posted at www.abigail-alliance.org. The opinion issued last year by the three-judge panel of the DC Federal Court of Appeals is provided in Attachment B. For more information on the status of the lawsuit see Attachment C, Drug Czars, editorial in the Wall Street Journal on May 4, 2007 by Steven Walker)*

Over those four years 2.2 million Americans died from cancer alone. This is not just a regulatory policy issue. It is a major civil rights issue.

Clinical Trial Registry Database

Turning to the discussion drafts, the Abigail Alliance has long sought readily available and more complete listings of clinical trials and access programs for investigational drugs, and we support the proposed clinical trials registry in the discussion draft.

Clinical Trial Results Database

We also support in concept, the idea of making the results of clinical trials public, but we think the clinical trial results database as proposed in the discussion draft has all the earmarks of a major regulatory misstep. The evidence for this can be found in the recent flap over Avandia. The publication of scientifically-weak, meta-analysis results in the New England Journal of Medicine was a statistical "drive-by" hit on the integrity of our regulatory system. If the results database is enacted as proposed, the FDA will become the regular target of poorly-constructed statistical hand-grenades, and spend far too much of its time trying to clean up the mess after each one explodes in sensational fashion in the media.

Consequently, we ask that the committee remove the clinical trial results database from the discussion draft, and schedule future hearings to receive additional input on how to make trial results public while at the same time preserving the integrity of our regulatory system.

Food and Drug Administration Advisory Panels Conflicts of Interest

On conflicts of interest on advisory committees, we think the draft legislation is putting the cart before the horse.

The Federal Advisory Committee Act prohibits inappropriate influence by the appointing authority over its advisory committees, but FDA review office directors are empowered to manipulate the ideological makeup of their advisory committees, and potentially use that power to pursue the outcome they want regarding policy matters and votes on specific drugs. We believe this has in fact happened with some cancer drugs. *(See Attachment D, Slides from Presentation to the Oncologic Drugs Advisory Committee, September 6, 2006, ODAC and the FDA, Arms-Length or Arm-In-Arm?, by Steven Walker; and Attachment C, Drug Czars, editorial in the Wall Street Journal, May 4, 2007, by Steven Walker)*

Congress should start by looking at the FDA's process for selecting advisory committee members and for now, table the secondary conflict of interest issue.

Risk Evaluation and Mitigation Strategies

We oppose the proposal to require mandatory risk evaluation and mitigation strategies, or REMS, because they are mandatory, making them yet another one-size-fits-all solution

that won't work. The FDA already has and uses the authority to impose what they call Risk Management Plans or RiskMAPs on drugs at the time of approval. RiskMAPs have so far been a mixed bag of prudent controls burdened with unnecessary approval delays and prescribing restrictions, coupled with requirements for highly-unethical post-approval clinical trials. RiskMAPs also have resulted in major intrusions by the FDA into the practice of medicine. Mandatory REMS, even though proposed as being flexible, are likely to evolve quickly into an over-applied defensive mechanism for FDA instead of its intended use of being a rational, sober post-marketing monitoring tool. We need, post-market monitoring of drugs, but we do not need any more one-size-fits-all solutions. We suggest that the flexible model for what must be included in a REMS be used to replace the current RiskMAP model, but that the need for a REMS be determined on a case-by-case basis.

The Reagan-Udall Institute for Applied Biomedical Research

We think the Udall-Reagan Institute is a good idea that could be made even better. The goal is regulatory modernization, and that can only come through real change in the way the FDA does it job. Consequently, the institute should be moved inside the FDA and given line authority to issue new policies and guidance, and to initiate rulemaking. *(For more information on the Abigail Alliance positions on what is wrong and how to modernize and improve the science and regulatory policies of the FDA, see Attachment E, Making FDA Work for Patients, Legal Backgrounder, Vol. 20, No. 10. Washington Legal Foundation., February 25, 2005; and Attachment F, Decelerated Approval,*

Presentation to the Oncologic Drugs Advisory Committee, by Steven Walker, November 8, 2005)

Closing Comments

This entire debate regarding FDA reform has its roots in a decades-old feud raging within the FDA and the medical research community between two groups of statisticians: those who believe in the forward-looking trials used for pre-approval testing, and those who support the backward-looking trials that try to find drug safety needles in haystacks.

Neither statistical camp should win this feud. Patients should win, and for that to happen, we need to move away from the rigid, often unethical statistical approaches we have now, and move toward real science.

We need to remember that FDA's mission is not to control and punish the drug companies, but rather to protect and promote the public health, and it is on the "promote" side where will find better treatments and cures for diseases like cancer.

I would like to close with an important fact. Every investigational drug for which the Abigail Alliance has sought early access was eventually approved by the FDA. We knew that patients would be better off if they could get the drug than if they could not, usually years before the FDA acted to make those drugs available. If the FDA was less a barrier

to progress, millions more would have gained access to that progress over the last seven years.

Thank you, and of course when the opening statements are concluded, I would be happy to answer your questions.

Attachment A

S.O.S to the FDA

Editorial in the Wall Street Journal
By Steven Walker

August 26, 2003

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August 26, 2003

COMMENTARY

S.O.S. to the FDA

By STEVEN WALKER
August 26, 2003

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Our Food and Drug Administration is often praised for establishing the "gold standard" for drug approvals. If it is FDA-approved, folks say, all can be sure that the drug has been rigorously shown to be safe and effective through years of careful review. Unfortunately, the people making this claim increasingly work at the FDA. Those waiting for FDA decisions, mainly dying patients and those who care for them, view the agency as a barrier to new treatments that they desperately need to live. The agency's inability to recognize and adjust to the accelerating pace of medical research has tarnished its gilt.

Never has this been more evident than now. At a recent major cancer research meeting in Chicago, two announcements were made regarding breakthrough drugs for colon cancer, the second leading cause of cancer deaths in the U.S. (According to the American Cancer Society it will kill 57,000 this year.) The first drug is Imclone Systems Inc.'s Erbitux, the not-so-new targeted drug that is inexplicably more famous for its ill-conceived rejection by the FDA in December 2001 and the ensuing scandals than for its effectiveness as a cancer drug.

Erbitux has once again been shown to be an important advance in treating colon cancer. Results of the latest trials are identical to the results the FDA rejected in 2001, and they more than meet the FDA's current standards for accelerated approval. Since the rejection, about 80,000 Americans have died from colon cancer without getting Erbitux. Erbitux shrank tumors for about 23% of patients for whom nothing else would work, and controlled the cancer for an average of four-plus months. Considering that the best FDA-approved treatment for colon cancer only controls tumors for about 10 months, adding this drug to the arsenal as a follow-up treatment is a major advance.

* * *

I know from direct observation how well Erbitux can work. Near death in September 2002, my wife Jennifer managed to enroll in a small clinical trial for Erbitux. The treatment lifted her off her deathbed in two days, resolved the symptoms of her cancer in two weeks, and allowed us to return to a normal life, skiing, hiking and working. Many patients in the trial experienced similar results. The sole side effect was a tolerable skin rash. Erbitux worked for six months. It stopped working in March this year. Out of accessible options to control her cancer, Jennifer died in June -- knowing that she was being denied access, by a plodding government agency, to even newer investigational drugs that might have further extended her life.

Another drug, whose results were kept secret by its sponsor and the FDA until the Chicago cancer

meeting in June, is Avastin, a drug developed by Genentech. It extends the effectiveness of the first-line treatment given to colon cancer patients by more than four months, and extends survival by four months too, with almost no increase in side-effects when given in combination with the approved first-line treatment known as the Saltz regimen. Although not yet comprehensively tested in late-stage, resistant cancer patients, Avastin might have been useful to Jennifer and thousands of others had they been able to try it in combination with other drugs.

So just like that, we now have the ability to extend the lives of colon cancer patients by an average of more than eight months (or in some cases longer), a significant increase when considering that advanced colon cancer patients can expect to live little more than a year. Tragically, patients can't get Erbitux or Avastin because of the FDA's antiquated approach to recognizing and approving cancer drugs. The key to availability of any new drug is approval by the FDA, and neither drug is likely to be approved sooner than early next year. The drugs can't be purchased for any price, and aren't available outside small clinical trials and a small expanded access program for Erbitux. The FDA has six months to review Avastin and Erbitux from the date they receive complete applications. The application for Erbitux was submitted on Aug. 14, and an application has yet to be submitted for Avastin. Before blaming the companies for the time they are taking to file their paperwork, understand that the FDA is a notoriously nitpicky agency, concentrating on the most minor details even when those are not relevant to those who will be treated with the drug. Americans shouldn't die, for example, because the FDA is hung up on a few words in the package labeling.

The great majority of those finding out they have advanced colon cancer in the coming months will not get Avastin with their first-line treatment, costing them an average of at least four months of life. Nearly all of those finding out that their cancers will no longer respond to the existing approved treatments will be denied access to Erbitux, costing them at least four months of control of their disease. Some might quickly blame the companies for not giving the drugs away, and the FDA will claim they would allow this if the companies would do it, but no company can afford to treat thousands of patients for free with drugs that cost hundreds of millions to develop, produce and administer.

So just like that, two significant victories in our war on cancer will be denied to cancer patients. Using a conservative estimate based on American Cancer Society numbers for new cases and deaths, and the clinical trial results, about 14,500 Americans will be denied Avastin and about 28,500 will be denied Erbitux over the next six months while the FDA waits for and processes paperwork, assuming it reviews the applications quickly, by no means a certain prospect. The cost in human life adds up to about 14,300 years. If approval takes longer the losses will mount. The actual cost in life will be further increased because off-label use for patients with other forms of cancer will also be precluded. The situation with Erbitux and Avastin is not isolated. It is business as usual.

At the FDA, the process and strict adherence to regulations, guidance and policy always comes first, and the agency's power over availability of drugs is absolute. My wife's battle with cancer and the setbacks she suffered at the hands of the system are typical of the challenges faced by all Americans fighting life-threatening diseases. Too many people are dying at the hands of a bureaucracy that does not have an approval mechanism that could ease the loss of life.

We at the Abigail Alliance for Better Access to Developmental Drugs and the Washington Legal Foundation have given them one. Called "Tier 1 Initial Approval," it lowers the barriers imposed on cancer patients by the FDA's gold standard. It would give the agency the ability to respond to those with immediate needs without weakening its ability to ensure that new drugs are safe and

effective. In fact, it would strengthen our drug development system, forcing it to be more responsive to the patients it exists to serve.

As Mark McClellan, the new FDA commissioner, continues his efforts to repair inherited problems with the regulatory process, he also should race to modernize his agency from the ground up. Doing less will render his agency incapable of keeping pace with accelerating medical breakthroughs that are already transforming the prospects of some ill Americans from despair, to hope, to life. Some will oppose him vigorously because old ways die hard.

We are finally beginning to win the war on cancer. The cancer patients have always been courageous foot soldiers in the fight, contributing mightily in clinical trials to get us here. It is now time to see if there are heroes at the FDA with the vision, courage and resolve to clean the tarnish from our gold standard. A lot of lives -- and very possibly yours -- depend on it.

Mr. Walker, adviser to the Abigail Alliance for Better Access to Developmental Drugs, is the husband of the late Jennifer I. McNeillie.

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Attachment B

Opinion of the

United States Court of Appeals
For the District of Columbia Circuit

Abigail Allianced v von Eschenbach

Decided May 2, 2006

Notice: This opinion is subject to formal revision before publication in the Federal Reporter or U.S.App.D.C. Reports. Users are requested to notify the Clerk of any formal errors in order that corrections may be made before the bound volumes go to press.

United States Court of Appeals

FOR THE DISTRICT OF COLUMBIA CIRCUIT

Argued October 21, 2005 Decided May 2, 2006

No. 04-5350

ABIGAIL ALLIANCE FOR BETTER ACCESS TO
DEVELOPMENTAL DRUGS AND
WASHINGTON LEGAL FOUNDATION,
APPELLANTS

v.

ANDREW C. VON ESCHENBACH, M.D.,
IN HIS OFFICIAL CAPACITY AS ACTING COMMISSIONER,
FOOD AND DRUG ADMINISTRATION AND
MICHAEL O. LEAVITT,
IN HIS OFFICIAL CAPACITY AS SECRETARY,
U.S. DEPT. OF HEALTH AND HUMAN SERVICES,
APPELLEES

Appeal from the United States District Court
for the District of Columbia
(No. 03cv01601)

James S. Ballenger argued the cause for appellants. With him on the briefs were *Daniel J. Popeo* and *David Price.*

Richard A. Samp entered an appearance.

Rhonda C. Fields, Assistant U.S. Attorney, argued the cause for appellee. With her on the brief were *Kenneth L. Wainstein*, U.S. Attorney, *Michael J. Ryan*, Assistant U.S. Attorney, *Eric M. Blumberg*, Deputy Chief Counsel, U.S. Department of Health and Human Services, and *Karen E. Schifter*, Associate Chief Counsel. *R. Craig Lawrence*, Assistant U.S. Attorney, entered an appearance.

Before: GINSBURG, *Chief Judge*, and ROGERS and GRIFFITH, *Circuit Judges*.

Opinion for the Court filed by *Circuit Judge* ROGERS.

Dissenting opinion filed by *Circuit Judge* GRIFFITH.

ROGERS, *Circuit Judge*: The Abigail Alliance for Better Access to Developmental Drugs ("the Alliance") seeks to enjoin the Food and Drug Administration ("FDA") from continuing to enforce a policy barring the sale of new drugs that the FDA has determined, after Phase I trials on human beings, are sufficiently safe for expanded human testing (hereafter "post-Phase I investigational new drugs"). More specifically, the Alliance seeks access to potentially life-saving post-Phase I investigational new drugs on behalf of mentally competent, terminally ill adult patients who have no alternative government-approved treatment options (hereafter "terminally ill patients"). The Alliance contends that the FDA's policy violates the substantive due process rights to privacy, liberty, and life of its terminally ill members. The complaint presents the question of whether the Due Process Clause protects the right of terminally ill patients to decide, without FDA interference, whether to assume the risks of using potentially life-saving investigational new drugs that the FDA has yet to approve for commercial

marketing but that the FDA has determined, after Phase I clinical human trials, are safe enough for further testing on a substantial number of human beings.

Upon applying the Supreme Court's test for addressing substantive due process claims set forth in *Washington v. Glucksberg*, 521 U.S. 702, 710 (1997), we hold that the district court erred in dismissing the Alliance's complaint pursuant to Federal Rule of Civil Procedure 12(b)(6) for failure to state a claim. First, the right at issue, carefully described, is the right of a mentally competent, terminally ill adult patient to access potentially life-saving post-Phase I investigational new drugs, upon a doctor's advice, even where that medication carries risks for the patient. Second, we find, upon examining "our Nation's history, legal traditions, and practices," *Glucksberg*, 521 U.S. at 710, that the government has not blocked access to new drugs throughout the greater part of our Nation's history. Only in recent years has the government injected itself into consideration of the effectiveness of new drugs. Third, Supreme Court precedent on liberty indicates that the right claimed by the Alliance can be inferred from the Court's conclusion in *Cruzan v. Director, Missouri Department of Health*, 497 U.S. 261, 278 (1990), that an individual has a due process right to refuse life-sustaining medical treatment, *id.* at 279. Here, the claim implicates a similar right — the right to access potentially life-sustaining medication where there are no alternative government-approved treatment options. In both instances, the key is the patient's right to make the decision about her life free from government interference.

Because the question remains whether the FDA's challenged policy has violated that right, we reverse the dismissal of the Alliance's complaint and remand the case to the district court to determine whether the FDA's policy "is narrowly tailored to serve a compelling [governmental]

interest." *Glucksberg*, 521 U.S. at 721 (quoting *Reno v. Flores*, 506 U.S. 292, 302 (1993)).

In Part I, we set forth the background to this appeal. In Part II, we examine Supreme Court precedent indicating how substantive due process rights are to be discerned. So guided, we consider, in Part III, whether the Alliance's claimed right warrants protection under the Due Process Clause.

I.

A.

The Food, Drug, and Cosmetic Act ("FDCA"), Pub. L. No. 75-717, §§ 1-902, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. § 301 *et seq.* (2000)), prohibits drug manufacturers from introducing any "new drug" into interstate commerce until manufacturers have applied for, and received, FDA approval. 21 U.S.C. § 355(a). A "new drug" is any substance covered by the FDCA not "generally recognized, among experts . . . as safe and effective for use under the conditions prescribed . . . in the labeling." 21 U.S.C. § 321(p)(1); *see also United States v. 50 Boxes More or Less*, 909 F.2d 24 (1st Cir. 1990). Before a new drug is eligible for full approval and marketing, the Secretary of the U.S. Department of Health and Human Services must find "substantial evidence that the drug will have the effect it purports or is represented to have." 21 U.S.C. § 355(d). Exempted from this general ban are new drugs "intended solely for investigational use by experts . . . ." *Id.* § 355(i)(1).

The FDCA directs the Secretary to promulgate regulations for testing new drugs. *Id.* Pursuant to this authority, the FDA has promulgated regulations that require three phases of government testing on humans before investigational new drugs can receive FDA approval and enter the commercial marketplace. In Phase I, new drugs are tested on 20 to 80

human subjects to determine "the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness." 21 C.F.R. § 312.21(a). It takes approximately one year to conduct Phase I testing.[1] FDA counsel acknowledged at oral argument that drugs that survive this phase have been deemed "sufficiently safe for substantial human testing, but [are] not yet proven to be safe and effective to the satisfaction of the FDA [to be commercially marketed]." Oral Argument Tape of Oct. 21, 2005 at 15:57-15:59. Phase II involves targeted, controlled clinical studies of up to several hundred human subjects "to evaluate the effectiveness of the [Phase I investigational new] drug . . . and to determine the common short-term side effects and risks associated with the drug." 21 C.F.R. § 312.21(b). Phase III expanded trials, which can include several thousand human subjects, are "performed after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug . . . ." *Id.* § 312.21(c). With narrow exceptions, FDA regulations require informed consent to be obtained from clinical trial participants. *Id.* §§ 50.1-50.27.

B.

On January 16, 2003, the Alliance submitted a proposal to the FDA for new regulations to render post-Phase I investigational new drugs available to terminally ill patients who were not admitted to the FDA's clinical trials. The FDA rejected the proposal by letter dated April 25, 2003, outlining the FDA's policy. On June 11, 2003, Alliance filed a Citizen Petition, pursuant to 21 C.F.R. § 10.30, challenging the FDA's

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[1] *See* Alison R. McCabe, *A Precarious Balancing Act—The Role of the FDA as Protector of Public Health and Industry Wealth*, 36 SUFFOLK U. L. REV. 787, 790 n.26 (2003).

policy barring the sale of investigational new drugs that have successfully completed Phase I trials to terminally ill patients not selected for clinical trials. The FDA acknowledged receipt of the Citizen Petition but otherwise did not respond within 180 days, thereby entitling the Alliance to seek judicial review of the challenged policy. *See id.* § 10.30(e)(2).

The Alliance filed suit against the FDA Commissioner and the Secretary of the Department of Health and Human Services, seeking to enjoin the FDA from enforcing the policy barring the sale of post-Phase I investigational new drugs to terminally ill patients not in Phase II clinical trials. Noting that the FDA has administrative discretion to define several stages for human testing of new drugs after animal testing has been conducted, the complaint alleges that it takes, on average, just under seven years for investigational new drugs to complete the three phases of clinical human trials and receive FDA approval for commercial marketing and thus become eligible for purchase by persons not in FDA clinical trials. Compl. ¶ 12.[2] The complaint also alleges that non-commercial options provide relief only to a very small number of terminally ill patients as spaces in clinical trials are "very limited . . . in relation to the need." Compl. ¶ 15. The Alliance asserts that clinical human trials are limited in number and by type of patient who qualifies. Further, the FDA's "compassionate use" programs, which permit drug companies voluntarily to provide new drugs at cost during the pre-approval period, are available only to "a fraction of those in desperate need." *Id.* Although the FDA may permit "treatment use" of unapproved new drugs, *see* 21 C.F.R. § 312.34 (1999), and has allowed access for limited groups of persons with

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[2] *See also* Christopher P. Adams & Van V. Brantner, *New Drug Development: Estimating Entry from Human Clinical Trials* 9 (July 7, 2003), *available at* http://www.ftc.gov/be/workpapers/wp262.pdf.

AIDS,[3] the FDA has refused as a general matter to allow terminally ill patients to have access to investigational new drugs that have successfully completed Phase I trials. Consequently, the complaint alleges, the effect of the FDA policy, as illustrated by the examples of the deaths of four terminally ill patients, has been to deny terminally ill patients the choice to use post-Phase I investigational new drugs despite the patients' willingness "to assume risks if their physicians advise them that a treatment may save or prolong their lives and if they have no other viable options." Compl. ¶¶ 16, 18. Prior to discovery, the FDA moved to dismiss the complaint, and, alternatively, for summary judgment. The Alliance responded by filing an opposition and its own motion for summary judgment.

The district court dismissed the complaint pursuant to Rule 12(b)(6) for failure to state a claim. The court rejected the Alliance's argument that it sought no "new" right but only recognition and enforcement of the right to life that is explicitly guaranteed by the Due Process Clause, observing that no court decision has "extended the Due Process Clause to cover a terminally ill patient's right to receive medical treatment." Mem. Op. of Aug. 30, 2004, at 18 (emphasis deleted). Although acknowledging "the Nation's longstanding legal tradition . . . to attempt to preserve life," *id.*, the district court stated that in *Glucksberg*, the Supreme Court had distinguished some "personal" decisions from others, 521 U.S. at 727, and that the Alliance could not "possibl[y] claim that the specific right claimed has a long-standing tradition." Mem. Op. at 18. The district court also rejected the Alliance's argument that the Supreme Court's recognition in *Cruzan* of the right to choose

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[3] *See* Michael D. Greenberg, *AIDS, Experimental Drug Approval, and the FDA New Drug Screening Process*, 3 N.Y.U. J. LEGIS. & PUB. POL'Y 295, 315-20 (1999-2000).

death by refusing medical treatment implied a complementary right to choose life by obtaining potentially life-saving medication. In the district court's view, the Alliance sought recognition of "an entirely different sort of right [from that recognized in *Cruzan*] — not freedom from government imposition, but an affirmative right of access to medical treatment." *Id.* at 19. In the absence of due process protection for terminally ill patients seeking access to potentially life saving post-Phase I drugs, the district court concluded that the challenged FDA policy is rationally related to a legitimate governmental interest.

The Alliance appeals, and our review is *de novo*.[4] *See Cicippio-Puleo v. Islamic Republic of Iran,* 353 F.3d 1024, 1031-32 (D.C. Cir. 2004). We treat the dismissal of the complaint as occurring pursuant to Rule 12(b)(6), notwithstanding the district court's consideration of the FDA's April 23, 2003 letter because the letter's conclusion was alleged in the complaint and the FDA does not dispute its contents. *See Gryl ex rel. Shire Pharms. Group PLC v. Shire Pharms. Group PLC*, 298 F.3d 136, 140 (2d Cir. 2002); *Pryor v. Nat'l Collegiate Athletic Ass'n*, 288 F.3d 548, 560 (3d Cir. 2002) (citing 62 Fed. Proc. L. Ed. § 62:508). *Cf. Settles v. United States Parole Comm'n*, 429 F.3d 1098, 1107 (D.C. Cir. 2005).

A court should not dismiss a complaint pursuant to Rule 12(b)(6) for failure to state a claim "unless it appears beyond doubt that the plaintiff can prove no set of facts in support of his claim which would entitle him to relief." *Conley v. Gibson*, 355 U.S. 41, 45-46 (1957); *Warren v. District of Columbia*, 353 F.3d 36, 37 (D.C. Cir. 2004). In determining the sufficiency of the

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[4] The Washington Legal Foundation is also a named appellant, but conceded at oral argument that it lacked Article III standing.

complaint, this court reviews questions of law *de novo* while treating the complaint's factual allegations as true and granting the plaintiff the benefit of all reasonable inferences from the facts alleged. *See Conley,* 351 U.S. at 45-46; *Sparrow v. United Air Lines, Inc.*, 216 F.3d 1111, 1114 (D.C. Cir. 2000).

II.

The Due Process Clause of the Fifth Amendment to the United States Constitution provides that "[n]o person shall be . . . deprived of life, liberty, or property, without due process of law." U.S. CONST. AMEND. V. The Supreme Court has held that the Clause "guarantees more than fair process" and accords substantive protection to the rights it guarantees. *See Troxel v. Granville*, 530 U.S. 57, 65 (2000) (plurality opinion); *Glucksberg*, 521 U.S. at 719; *Flores*, 507 U.S. at 301-02. Substantive due process claims can present difficulties for courts. *See Michael H. v. Gerald D.*, 491 U.S. 110, 121 (1989) (plurality opinion); *Moore v. City of East Cleveland*, 431 U.S. 494, 502 (1977). In a case of first impression where fundamental rights may be at stake, determining the limits of the government's authority over an individual's freedom to make certain personal decisions unavoidably entails a careful and possibly arduous assessment of that personal decision's objective characteristics in order to determine whether it warrants protection under the Due Process Clause. *Cf. Roberts v. U.S. Jaycees*, 468 U.S. 609, 620 (1984). Nonetheless, the district court appears to have viewed its role as unduly constrained. Pointing to an advisory cautioning in *Dronenburg v. Zech*, 741 F.2d 1388, 1396 (D.C. Cir. 1984), that lower courts "should [not] freely create new constitutional rights" without "guidance from the Constitution or . . . from articulated Supreme Court principle," the district court focused on the absence of binding precedent recognizing the substantive due process right claimed by the Alliance. Since *Dronenberg,* the Supreme Court

has provided guideposts to enable a court to assess the merits of the Alliance's claim.[5]

Although the Supreme Court has never explicitly said so, and we need not decide the matter here, it appears the Supreme Court has employed two distinct approaches when faced with a claim to a fundamental right. In some cases, the Court has discerned the existence of fundamental rights by probing what "personal dignity and autonomy" demand. *See Planned Parenthood of Southeastern Pa. v. Casey*, 505 U.S. 833, 851 (1992) (citations omitted). In other cases, the Court has derived fundamental rights by reference to the Nation's history and legal tradition, *see, e.g., Glucksberg*, 521 U.S. 702.[6] The line of cases beginning with *Griswold v. Connecticut*, 381 U.S. 479 (1965), and continuing through *Eisenstadt v. Baird*, 405 U.S. 438 (1972), *Roe v. Wade*, 410 U.S. 113 (1973), and *Casey*, 505 U.S. 833, follow the first approach with their heavy reliance on the concepts of individual rights to autonomy and self-determination, and in their unwillingness to countenance state intrusion into certain protected domains such as the bedroom, the clinic, and the womb. This approach is succinctly captured by *Casey*'s characterization of substantive due process rights as those that involve "the most intimate and personal choices a person may make in a lifetime, choices central to personal dignity and autonomy." *Casey*, 505 U.S. at 851.

The other approach for determining whether a claimed right

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[5] The dissent, to the extent it presupposes the only liberties protected by the Constitution are those that have been explicitly recognized by the Supreme Court, *see* Dissent at 13 & n.3, is in error.

[6] *See* Robert C. Post, *The Supreme Court, 2002 Term—Foreword: Fashioning the Legal Constitution: Culture, Courts, and Law*, 117 HARV. L. REV. 4, 89 (2003).

warrants substantive due process protection, which appears to be more restrictive,[7] has two "features." *See Glucksberg*, 521 U.S. at 720. Under *Glucksberg*, courts must inquire whether the fundamental right asserted is "objectively, 'deeply rooted in this Nation's history and tradition,'" *id.* at 721 (quoting *Moore*, 431 U.S. at 503; *Snyder v. Massachusetts*, 291 U.S. 97 (1934)),[8] and

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[7] Post, *supra* note 6, at 91-93; Laurence H. Tribe, Lawrence v. Texas: *The "Fundamental Right" That Dare Not Speak its Name*, 117 HARV. L. REV. 1893, 1921-23 (2004).

[8] The Supreme Court's mention in *Lawrence v. Texas*, 539 U.S. 558, 592 (2003), of the "emerging awareness" regarding the liberty to engage in homosexual conduct does not limit the swath of time to be surveyed in a *Glucksberg* analysis of history and tradition. The reference to "laws and tradition in the past half century" appears in support of the Court's decision to depart from stare decisis and overrule *Bowers v. Hardwick*, 478 U.S. 186 (1986). Discrediting *Bowers*'s "sweeping references" to history thus had a purpose in addition to that addressed by the *Glucksberg* analysis: it is intended to show that not only had the Court in *Bowers* misread history but that it also had ignored modern trends giving protection to conduct that had long avoided criminal proscription in the states. *See Lawrence,* 539 U.S. at 568. Reading *Lawrence* as narrowing the *Glucksberg* historical inquiry to the last half century would gut the purpose of the *Glucksberg* test, which is to prevent the creation of substantive due process rights by forcing courts to accord due process protection only to those rights with a strong foundation in tradition. Other circuits have either treated the *Glucksberg* analysis as controlling after *Lawrence, see Fields v. Palmdale School Dist.*, 427 F.3d 1197 (9th Cir. 2005); *Fields v. Legacy Health System*, 413 F.3d 943 (9th Cir. 2005); *Doe v. City of Lafayette, Ind.*, 377 F.3d 757, 768 (7th Cir. 2004), or viewed *Lawrence* as not, properly speaking, a substantive due process decision, *see Lofton v. Sec'y of Dep't of Children and Family Servs.*, 358 F.3d 804, 815-16 (11th Cir. 2004); *Muth v. Frank*, 412 F.3d 808, 818 (7th Cir. 2005). No court has regarded *Lawrence* as cabining *Glucksberg.*

"implicit in the concept of ordered liberty, such that neither liberty nor justice would exist if [it] were sacrificed," *Glucksberg*, 521 U.S. at 721 (quoting *Palko v. Connecticut*, 302 U.S. 319, 325-26 (1937)) (internal quotation marks omitted). Additionally, in order to ensure that courts do not multiply rights without principled boundaries, courts must provide a "careful description of the fundamental liberty interest." *Id.* at 721-23. If a court concludes that the claimed right is a fundamental right entitled to protection under the Due Process Clause, then the burden shifts to the government to show that its encroachment upon the right "is narrowly tailored to serve a compelling [governmental] interest." *Id.* at 721 (quoting *Flores*, 507 U.S. at 302).

Because we conclude, upon applying the seemingly more restrictive analysis of *Glucksberg*, that the claimed right warrants protection under the Due Process Clause, we need not decide whether the line of cases construing the concept of "personal dignity and autonomy" would also lend protection to the claimed right.

III.

The question presented by the Alliance's complaint is whether the Due Process Clause protects the right of terminally ill patients to make an informed decision that may prolong life, specifically by use of potentially life-saving new drugs that the FDA has yet to approve for commercial marketing but that the FDA has determined, after Phase I clinical human trials, are safe enough for further testing on a substantial number of human beings. The Due Process Clause, as *Glucksberg* makes clear, protects those liberties "deeply rooted in this Nation's history and tradition." 521 U.S. at 721 (citation omitted). The Supreme Court has variously referred to these rights as principles "so rooted in the traditions and conscience of our people as to be

ranked as fundamental," *Snyder*, 291 U.S. at 105, and as immunities "implicit in the concept of ordered liberty," *Palko*, 302 U.S. at 325. Thus, a court's examination of our Nation's history and tradition cannot be based on so specific a description of the claimed right as would undercut the interests protected by the Due Process Clause.

A.

One feature of the *Glucksberg* analysis requires courts to compose a "careful description" of the asserted fundamental liberty interest before extending due process protection to it. 521 U.S. at 721. The Supreme Court has not settled on how precisely formulated the right must be. Two Justices have interpreted the "careful description" requirement as indicating that courts should identify fundamental rights at the "most specific level at which a relevant tradition protecting, or denying protection to, the asserted right can be identified." *Michael H.*, 491 U.S. at 127 n.6 (1989) (Scalia, J., with Rehnquist, C.J., concurring). Two other Justices have indicated that asserted rights not expressed at "'the most specific level' [of generality] available" can nonetheless be recognized. *Id.* at 132 (O'Connor and Kennedy, JJ., concurring). The "careful description" requirement was first invoked by the Court in *Flores*, 507 U.S. at 302 (1993), which relied on *Collins v. City of Harker Heights*, 503 U.S. 115, 125 (1992), where the notion of careful description was expressed as a pleading requirement. Since *Glucksberg*, the Court has applied this requirement once without elaboration. *See Chavez v. Martinez*, 538 U.S. 760, 775-76 (2003).

In *Hutchins v. District of Columbia*, 188 F.3d 531 (D.C. Cir. 1999), the en banc court applied the careful description requirement in its substantive due process analysis. The court viewed the careful description requirement as a means of constraining the inadvertent creation of rights that could fall

within the scope of loosely worded descriptions and thus threaten the separation of powers. *See id.* at 542-45. Despite reaching different conclusions about the appropriate level of generality in describing the claimed right, *compare id.* at 538 (citing *Michael H.*, 491 U.S. at 127 n.6 (Scalia, J., with Rehnquist, C.J., concurring), *with id.* at 555-57 (Rogers, J., dissenting) (citing *Moore,* 431 U.S. at 502-03), the court concluded that the animating principle underlying the careful description requirement is that courts should proceed with care in examining substantive due process claims. *See id.* at 538.

The Alliance's complaint contains the careful description we seek, allowing this court to consider whether the challenged FDA policy impinges upon one or more of the interests protected by the Due Process Clause. The FDA characterizes the Alliance's claimed right as a broadly stated prerogative to access post-Phase I investigational new drugs and to receive treatment, but the Alliance has defined the right more narrowly. The Alliance claims neither an unfettered right of access to all new or investigational new drugs nor a right to receive treatment from the government or at government expense. The Alliance's claim also does not challenge the Controlled Substances Act, 21 U.S.C. §§ 801 *et seq.*, or the government's authority to regulate substances deemed harmful to public health, safety, and welfare. Rather, the Alliance contends that the fundamental due process rights to privacy, liberty, and life include the right of terminally ill patients, acting on a doctor's advice, to obtain potentially life-saving medication when no alternative treatment approved by the government is available. Recognizing that the effectiveness and side effects of the investigational new drugs may still be in question after the Phase I trials have been completed, the Alliance asks only that the decision to assume these known or unknown risks be left to the terminally ill patient and not to the FDA. This description of the claimed right conforms to the demands of even the narrowest interpretation of the *Glucksberg*

B.

The other feature of the *Glucksberg* inquiry requires courts

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determine in the first instance whether FDA restrictions on a terminally ill patient's right of access to potentially life-saving medication that has cleared FDA Phase I trials are narrowly tailored to serve a compelling governmental interest. *See* Opinion at 30. At that time, the governmental interests will be identified by the FDA. The dissent oscillates between ignoring that this issue remains to be resolved, *see* Dissent at 9, and asserting that the issue is incapable of resolution, *see id.* at 24. Performing strict scrutiny is not a task that Article III courts have historically regarded as "impossible." *But see* Dissent at 24.

Third, the dissent suggests that the court paves the way for medicinal use of marijuana. *See* Dissent at 14, 24. There is no slippery slope from finding a right of access to potentially life-saving investigational new drugs that have cleared FDA Phase I trials for safety to finding a right of access to illegal narcotics. Marijuana is listed as a Schedule I substance under the Controlled Substances Act. A drug is included in Schedule I if it "has a high potential for abuse," "has no currently accepted medical use in treatment in the United States," and has "a lack of accepted safety for use . . . under medical supervision." 21 U.S.C. §§ 812(b)(1)(A)-(C). The investigational new drugs that have cleared FDA Phase I trials do not possess these attributes or the FDA would not be permitting their medical use in treatment, under medical supervision, by Phase II trial participants. Nothing in the court's holding supports the dissent's inference that marijuana, or any other Schedule I substance, if tested, would qualify for Phase I clearance and be potentially life-saving. By the same token, the record does not imply that a right of access exists to "federally-funded stem cell research and treatment." Dissent at 24. That issue is not before the court and the considerations that would be relevant under *Glucksberg* are not obviously similar. *See infra* n.26.

to determine whether there exists a long-standing tradition in our Nation that would protect individual access to potentially life-saving medication. Courts must focus on discerning those constitutionally protected interests whose existence can be inferred from the Due Process Clause and Supreme Court precedent construing the Clause. *See Cruzan*, 497 U.S. at 278. Although it is relevant to the substantive due process analysis that the government has never proscribed the desired conduct, this is not dispositive. The absence of regulation could be attributable to a liberty interest that is deeply rooted in this Nation's history and tradition, and therefore characterized by a history of liberty from governmental interference, but there may be another explanation. For example, a lack of regulation might indicate only that the technology of yesteryear did not warrant it.

The FDA's discussion of the merits of this question consists of a single sentence: "[The] FDA has had statutory authority to regulate drugs for almost a century, and that authority is now firmly ingrained in our understanding of the appropriate role of government." Appellee's Br. at 19.[10] We offer the following observations, mindful of the fact that the Alliance is complaining only of obstacles to post-Phase I investigational new drugs erected by the FDA and not obstacles that might be

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[10] The FDA argues in its brief that the Alliance never argued in the district court that drugs were unregulated for most of our Nation's history, and thus cannot raise this argument for the first time on appeal. In fact, the Alliance argued in district court that *Glucksberg* supported its due process claim, *see* Pls.' Cross-Mot. at 8-9, and the district court relied on the *Glucksberg* analysis in dismissing the complaint. As the FDA states in its brief, whether the Alliance has asserted a fundamental right is a legal issue on which this court is fully briefed. There is no reason why the analysis cannot proceed.

erected by state consumer protection or other laws.[11]

A right of control over one's body has deep roots in the common law. The venerable commentator on the common law William Blackstone wrote that the right to "personal security" includes "a person's legal and uninterrupted enjoyment of his life, his limbs, his body, [and] his health," as well as "the preservation of a man's health from such practices as may prejudice or annoy it." WILLIAM BLACKSTONE, 1 COMMENTARIES *125, *130. This right included the right to self-defense and the right to self-preservation. "For whatever is done by a man, to save either life or member, is looked upon as done upon the highest necessity and compulsion." *Id.* at *127. As recognized throughout Anglo-American history and law, when a person is faced with death, necessity often warrants extraordinary measures not otherwise justified. Indeed the principle holds even when that action impinges upon the rights of others. *See, e.g.*, *Ploof v. Putnam*, 81 Vt. 471, 475 (1908) ("This doctrine of necessity applies with special force to the preservation of human life. . . . One may sacrifice the personal property of another to save his life or the lives of his fellows.") (internal citation omitted); *Mouse's Case*, 77 Eng. Rep. 1341, 1342 (K.B. 1609) (deciding that it is lawful to throw overboard property of another for safety of lives of passengers); RESTATEMENT (FIRST) OF TORTS § 197 (1934); *see generally* George C. Christie, *The Defense of Necessity Considered from the Legal and Moral Points of View*, 48 DUKE L. J. 975 (1996). *But see The Queen v. Dudley and Stephens*, 14 Q.B.D. 273 (1884) (holding that the defense of necessity did not justify

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[11] The FDCA does not regulate doctors in their practice of medicine; they are licensed by the states. *See Chaney v. Heckler*, 718 F.2d 1174, 1179 (D.C. Cir. 1983), *rev'd on other grounds*, *Heckler v. Chaney*, 470 U.S. 821 (1985). *See also Gonzales v. Oregon*, 126 S. Ct. 904, 922-23 (2006).

taking of innocent life). Barring a terminally ill patient from the use of a potentially life-saving treatment impinges on this right of self-preservation.

Such a bar also puts the FDA in the position of interfering with efforts that could save a terminally ill patient's life. Although the common law imposes no general duty to rescue or to preserve a life, it does create liability for interfering with such efforts. Section 326 of the Restatement (First) of Torts, first published in 1934, explained that

> [o]ne who, without a privilege to do so, intentionally prevents a third person from giving to another aid necessary to his bodily security, is liable for bodily harm caused to the other by the absence of aid which he has prevented the third person from giving.

While infrequently invoked, this common law rule is of venerable vintage. *See id.*; *see also Soldano v. O'Daniels,* 190 Cal. Rptr. 310, 313, 316-18 (Ct. App. 1983); *Miller v. Arnal Corp.*, 632 P.2d 987, 993 (Ariz. App. 1981).[12]

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[12] As the dissent notes, fundamental rights may "not [be] simply deduced from abstract concepts of personal autonomy." Dissent at 10 (quoting *Glucksberg*, 521 U.S. at 725). Were it impermissible to draw any inferences from a broader right to a narrower right, however, nearly all of the Supreme Court's substantive due process case law would be out of bounds. *See, e.g.*, *Griswold*, 381 U.S. at 484-86 (inferring specific right to use contraception from general right to be free from intrusion into "sacred precincts of marital bedrooms"); *Roe*, 410 U.S. 113 (identifying specific right to terminate a pregnancy from broader right to privacy); *Moore*, 431 U.S. at 503 (extrapolating from broader constitutional protection for "the sanctity of the family" to specific right to determine extended family living arrangements). In any event, the court's holding is not grounded in the abstract notion of personal autonomy but rather in the specific

In contrast to these ancient principles, regulation of access to new drugs has a history in this country that is of recent origin. Prior to 1906, there was essentially no drug regulation in the United States.[13] In that year Congress enacted the Pure Food and Drug Act ("1906 Act"), Pub. L. No. 59-384, 34 Stat. 768 (repealed 1938), which prohibited misbranded and adulterated foods or drugs from entering interstate commerce, 34 Stat. at 768, and prohibited false and misleading labeling, *id.* at 770.

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right to act in order to save one's own life.

[13] *See* Charles J. Walsh & Alissa Pyrich, *Rationalizing the Regulation of Prescription Drugs and Medical Devices: Perspectives on Private Certification and Tort Reform,* 48 RUTGERS L. REV. 883, 890-91 (1996); Note, *The Catch-22 for Persons with AIDS: To Have or Not To Have Easy Access to Investigational Therapies and Early Approval for New Drugs*, 69 S. CAL. L. REV. 105, 109 (1995); *see also Gonzales v. Raich,* 125 S. Ct. 2195, 2202-03 (2005). The FDA Historian Wallace F. Janssen writes that prior to 1906 was the "heyday of 'patent medicines,'" a time when "[a]nyone, no matter how ignorant or unqualified, could go into the drug manufacturing business" and when "[m]edicines . . . were sold without restriction at almost every crossroads store." Wallace F. Janssen, *Outline of the History of U.S. Drug Regulation and Labeling*, 36 FOOD DRUG COSM. L. J. 420, 422 (1981) ("*Outline of the History*"). He further recounts that in "colonial days, and long afterward, consumers . . . were their own food and drug inspectors," "there was a striking absence of statutes dealing with drugs," and, although there were food inspection laws and standards for weights and measures, *see id.* at 423, 425, "drug laws were virtually non-existent." Janssen, *America's First Food and Drug Laws,* 30 FOOD DRUG COSM. L. J. 665, 669, 671 (1975). This suggests that in this country's early history there were no restrictions on a patient's access to potentially life-saving medication, regardless of whatever restrictions may have been placed on physicians, pharmacists, apothecaries, poisons, or misbranded or adulterated substances. *See id.* at 669-72; Janssen, *Outline of the History*, at 426-28. *But cf.* Dissent at 15-17.

For a small number of particularly dangerous drugs, the 1906 Act required the labels to identify the drug's ingredients and quantities. *Id.* The statute also authorized the Bureau of Chemistry, a predecessor of the FDA, to seize nonconforming goods and to recommend federal prosecution of those who violated the 1906 Act. *Id.* at 769 § 4. The 1906 Act did not, however, limit individual access to new drugs or regulate therapeutic claims by drug manufacturers. *Cf. United States v. Johnson*, 221 U.S. 488 (1911). It thus appears that a patient still could obtain access to any new drug for medicinal use, even if the drug had no therapeutic benefit, albeit subject to the controls placed on narcotics in 1914 by the Harrison Narcotic Act. Act of Dec. 17, 1914, 38 Stat. 785.[14]

In 1938, Congress enacted the FDCA in response to the deaths of more than one hundred people, many of them children, from ingesting Elixir Sulfanilamide, which had been marketed as an antibiotic. *See* Report of the Secretary of Agriculture on Deaths Due to Elixir Sulfanilamide, S. Doc. No. 124, 75th Cong., 2d Sess. 1, 1-3 (1937) ("1937 Report").[15] For the first time, Congress required that drug manufacturers test, and the FDA review, all new drugs for safety prior to their commercial distribution. Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. §§ 301 *et seq.*); 1937 Report at 1-3. Under the 1938 Act, a new drug could be commercially

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[14] *See generally* James L. Zelenay, Jr., *The Prescription Drug User Fee Act: Is a Faster Food and Drug Administration Always a Better Food and Drug Administration?*, 60 FOOD & DRUG L.J. 261, 263-64 (2005); Steven R. Salbu, *Regulation of Drug Treatments for HIV and AIDS: A Contractarian Model of Access,* 11 YALE J. ON REG. 401, 406-09 (1994); *cf. State of Minnesota ex rel. Whipple v. Martinson*, 256 U.S. 41, 45 (1921).

[15] *See* Salbu, *supra* note 14, at 407.

marketed only after the manufacturer filed a New Drug Application ("NDA") with the FDA that set forth medical and scientific information attesting to the drug's safety. The 1938 Act did not, however, require drug manufacturers to receive affirmative FDA approval before marketing the drug.[16] Rather, an NDA became automatically effective within a time frame set by the FDA unless the FDA determined that the drug was unsafe and barred its commercial distribution.[17] It was not until 1951, in the Durham-Humphrey Amendment, that Congress created the category of prescription drugs, i.e., drugs that are unsafe for self-medication but which can be used while under a doctor's supervision. *See* Act of Oct. 25, 1951, 65 Stat. 648 (1951) (codified at 21 U.S.C. § 353(b)).

Only in 1962 did Congress require drug manufacturers to provide empirical evidence of the effectiveness of a drug as opposed to merely the drug's safety.[18] The Kefauver-Harris Amendments, Pub. L. No. 87-781, 76 Stat. 780 (1960) (codified in scattered sections of 21 U.S.C. §§ 301-81 (1982 & Supp. IV 1986)), were enacted in response to the rash of birth defects discovered in babies whose mothers had taken Thalidomide to ease morning sickness caused by pregnancy.[19] The Kefauver-Harris Amendments transformed drug regulation and the approval process in several respects. First, the Amendments required the FDA to review a new drug for both safety and effectiveness and specified that to demonstrate effectiveness

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[16] *See* Zelenay, *supra* note 14, at 264-65.

[17] *Id.*

[18] *See* Greenberg, *supra* note 3, at 295, 300 & n.23.

[19] *See* Salbu, *supra* note 14, at 408 n.41; *see generally* HARVEY TEFF & COLIN R. MUNRO, THALIDOMIDE: THE LEGAL AFTERMATH 1-10 (1976); Janssen, *Outline of the History*, at 438.

manufacturers were required to submit data from "adequate and well-controlled investigations." 21 U.S.C. § 355(d). Second, the Amendments authorized the FDA to approve human clinical trials, regulate drug advertising, inspect drug-manufacturing facilities, and promulgate good manufacturing practices. The Amendments also required drug manufacturers to disclose to the FDA any information they received regarding the adverse consequences of approved drugs.[20] This legislation set the framework for the system of drug regulation currently in place.

Despite the increased federal scrutiny of new drugs, important aspects of patient access to drugs are unregulated by the government and appear always to have been unregulated. "The FDA's regulatory authority extends to manufacturers of drugs but not to the physicians who dispense them."[21] Thus, a doctor may prescribe a drug to a patient for a purpose other than that for which the FDA has approved the use of the drug. Such "off-label" use may occur even if the drug is not deemed safe or effective for that use. Further, it appears that the FDA has never prohibited either off-label prescription or off-label use of drugs.[22] In recent years, the FDA has been moving to permit drug manufacturers to promote the use of their drugs for off-label purposes in limited circumstances.[23] *See* Food and Drug Administration Modernization Act of 1997, Pub. L. No.

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[20] *See* Walsh & Pyrich, *supra* note 13, at 901; *see also* Zelenay, *supra* note 14, at 266.

[21] Steven R. Salbu, *Off-Use, Prescription, and Marketing of FDA-Approved Drugs: An Assessment of Legislative and Regulatory Policy*, 51 FLA. L. REV. 181, 189-92 (1999). *See Chaney*, 718 F.2d at 1180.

[22] *See* Salbu, *supra* note 21, at 189-92.

[23] *See id.* at 211.

105-115, 111 Stat. 2296 (codified in scattered sections of 21 U.S.C. §§ 301-81).

For over half of our Nation's history, then, until the enactment of the 1906 Act, a person could obtain access to any new drug without any government interference whatsoever. Even after enactment of the FDCA in 1938, Congress imposed no limitation on the commercial marketing of new drugs based upon the drugs' effectiveness. Rather, at that time, the FDA could only interrupt the sale of new drugs based on its determination that a new drug was unsafe. Government regulation of drugs premised on concern over a new drug's efficacy, as opposed to its safety, is of recent origin. And even today, a patient may use a drug for unapproved purposes even where the drug may be unsafe or ineffective for the off-label purpose. Despite the FDA's claims to the contrary, therefore, it cannot be said that government control of access to potentially life-saving medication "is now firmly ingrained in our understanding of the appropriate role of government," Appellee's Br. at 19, so as to overturn the long-standing tradition of the right of self-preservation.[24]

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[24] The court does not, as the dissent suggests, "infer[] a constitutional right to be free from regulation" from "the lack of federal regulation" in this area prior to the recent past. *See* Dissent at 14. Rather, the court infers the right from the Due Process Clause and Supreme Court precedents construing the Due Process Clause. *See supra* n. 12. The fundamental right to take action, even risky action, free from government interference, in order to save one's own life undergirds the court's decision. Our point is that the relatively short-lived history of drug regulation, particularly as regards the effectiveness of a new drug, is not, as the dissent suggests, sufficient to establish that the government has acquired title to this right by adverse possession. The same logic plainly would not serve to establish a right to recreational drugs merely because, in the grand sweep of the Nation's history, these regulations are of relatively recent

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The Alliance's claim also falls squarely within the realm of rights the Supreme Court has held are "implicit in the concept of ordered liberty." *Palko*, 302 U.S. at 325. Specifically, the claimed right is implied by the Court's conclusion in *Cruzan* that due process protects a person's right to refuse life-sustaining treatment. *See Cruzan*, 497 U.S. at 279. Writing for the Court, Chief Justice Rehnquist noted in examining the origins of the doctrine of informed consent that the Court had observed early on that "[n]o right is held more sacred, or is more carefully guarded, by the common law, than the right of every individual to the possession and control of his own person, free from all restraint or interference of others, unless by clear and unquestionable authority of law." *Id.* at 269 (quoting *Union Pacific R. Co. v. Botsford*, 141 U.S. 250, 251 (1891)). The Court reasoned that "[t]he logical corollary of the doctrine of informed consent is that the patient generally possesses the right not to consent, that is, to refuse treatment." *Id.* at 270. Confronting for the first time what it described as a "perplexing question with unusually strong moral and ethical overtones," *id.* at 277, the Court turned to the language of the Fourteenth Amendment and its precedent to determine whether "the United States Constitution grants what is in common parlance referred to as a 'right to die,'" *id.* The Court reasoned that "[t]he principle that a competent person has a constitutionally protected liberty interest in refusing unwanted medical treatment may be inferred from our prior decisions." *Id.* Without qualification, the Court stated: "It cannot be disputed that the Due Process Clause protects an interest in life as well as an interest in refusing life-sustaining medical treatment." *Id.* at 281.

A similar analysis leads to the conclusion that the Due

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vintage.

Process Clause protects the liberty interest claimed by the Alliance for its terminally ill members. *See supra* Part III.A. The text of the Due Process Clause refers to protecting "liberty" and "life." Although there is no similarly clear textual basis for a "right to die" or refusing life-sustaining medical treatment, the Supreme Court in *Cruzan* recognized, in light of the common law and constitutionally protected liberty interests based on the inviolability of one's body, that an individual has a due process right to make an informed decision to engage in conduct, by withdrawing treatment, that will cause one's death.[25] The logical corollary is that an individual must also be free to decide for herself whether to assume any known or unknown risks of taking a medication that might prolong her life.

Like the right claimed in *Cruzan*, the right claimed by the Alliance to be free of FDA imposition does not involve treatment by the government or a government subsidy. Rather, much as the guardians of the comatose patient in *Cruzan* did, the Alliance seeks to have the government step aside by changing its policy so the individual right of self-determination is not violated. The Alliance claims that there is a protected right of terminally ill patients to choose to use potentially life-saving investigational new drugs that have successfully cleared Phase I. If there is a protected liberty interest in self-determination that includes a right to refuse life-sustaining treatment, even though this will hasten death, then the same liberty interest must

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[25] It was only in the course of balancing an individual's liberty interest against the relevant government interests that the Court indicated "the dramatic consequences involved in the refusal of [life-sustaining] treatment would inform the inquiry as to whether the deprivation of that interest is constitutionally permissible." *Cruzan*, 497 U.S. at 279. The Court's holding allowed the government to protect the autonomous exercise of the right to refuse life-sustaining treatment; it did not undermine the right.

include the complementary right of access to potentially life-sustaining medication, in light of the explicit protection accorded "life."[26] Our reasoning is not unlike that of the Supreme Court in *Eisenstadt*, 405 U.S. 438, where the Court held that the right to be free from unwanted government intrusion into the fundamental decision whether to have children establishes a right of access to contraception.

Contrary to the FDA's position, nothing in this court's precedent or that of the other circuit courts of appeal conflicts with our analysis. Although the district court concluded, in reliance upon our decision in *Dronenberg*, 741 F.2d at 1396, that lower courts may not consider claims to new substantive due process rights and principles not previously identified by the

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[26] The dissent fails to see how the court can reason from a right to refuse life-saving treatment to a right of access to life-saving treatment, *see* Dissent at 17-18, but the two go hand in hand. In either instance — refusal or access — the key is the patient's right to make her own decision free from government interference. Moreover, the right of access to investigational new drugs that have cleared Phase I trials is different from and does not imply a general right to receive life-saving treatment, as the dissent, Dissent at 24, and the district court presumed. Nor does the court reach the question whether there is such a right for that is not the Alliance's claim.

Finally, the dissent mistakenly suggests the court offends the "concept of ordered liberty" because the court's decision is "contrary to the expressed will of Congress and the Executive and to the deference courts owe to the democratic branches on such controversial matters." Dissent at 22-23. Although the term "ordered liberty" necessarily remains somewhat unclear, it cannot stand for a broad principle of deference to the political branches whenever "unknown questions of science" are involved. *See id.* Otherwise, it would establish a zone in which the political branches would be free to regulate persons unconstrained by the individual liberties preserved in the Constitution.

Supreme Court, *see supra* page 9, this court has addressed substantive due process claims on a number of occasions. *See, e.g., N.Y. State Opthalmological Soc'y v. Bowen*, 854 F.2d 1379 (D.C. Cir. 1988). Most pertinently, in *Butera v. District of Columbia*, 235 F.3d 637 (D.C. Cir. 2001), the court confronted, in the context of a qualified immunity defense, the claim of a substantive due process right to life, personal security, and bodily integrity. *Butera* involved a suit under 42 U.S.C. § 1983 brought by the mother of a man who was shot while working undercover for the police department. The court in *Butera* did not suggest that the advisory admonition in *Dronenberg*, 741 F.2d at 1396, precluded either the substantive due process inquiry or the conclusion that a fundamental right was implicated.

The decisions in the other circuits on which the FDA relies likewise fail to support its position that there is no substantive due process right of access to potentially life-saving treatment. *United States v. Burzynksi Cancer Research Institute*, 819 F.2d 1301 (5th Cir. 1987), which held that the doctor and patient had not stated a constitutional tort based on the allegedly improper seizure of the doctor's patient records and thus that they did not overcome the defendant's claim of qualified immunity, *id.* at 1310-11, bears no legal or factual relevance to the question before this court. The statement in *Carnohan v. United States,* 616 F.2d 1120, 1122 (9th Cir. 1980), that "[c]onstitutional rights of privacy and personal liberty do not give individuals the right to obtain [the cancer drug] laetrile free of the lawful exercise of government police power," was dictum; the Ninth Circuit never reached the merits of the claimed fundamental right of access as the complaint was dismissed for failure to exhaust administrative remedies.

Further, as the Alliance pointed out in its brief, the terminally ill patients in *Rutherford v. United States*, 616 F.2d

455 (10th Cir. 1980), like those in *Carnohan*, sought access to laetrile, a new cancer drug that had not cleared FDA's Phase I safety hurdle and thus had not been approved for expanded testing on humans in ongoing clinical trials, *see id.* at 456-57. The Tenth Circuit rejected a right to laetrile, reasoning that the choice of a particular treatment or medication is "within the area of governmental interest in protecting public health." *Id.* at 457. Of course, the government's interest in regulating has no bearing upon the identification of a fundamental right. Rather, its interest is to be considered only if, and after, a court recognizes a fundamental right; at that point, the burden shifts to the government to demonstrate a narrowly tailored "compelling interest" in burdening that right. Because the FDA had neither eliminated the possibility that laetrile was a poison nor approved the drug for basic human testing in Phase I trials, the government's interest in *Rutherford* might well have been sufficiently compelling to warrant restricting access to the drug. In this case, the government's interest may prove to be weaker because the Alliance seeks only access to investigational new drugs that the FDA, after Phase I human trials, has deemed sufficiently safe for human testing on a substantial number of human beings. In other words, the Alliance seeks for its members the same right of access enjoyed by those terminally ill patients lucky enough to secure a spot in Phase II trials.

Accordingly, we hold that the district court erred in dismissing the Alliance's complaint pursuant to Rule 12(b)(6) for failure to state a claim. We conclude, upon applying the *Glucksberg* analysis and heeding the protected liberty interests articulated by the Supreme Court, that where there are no alternative government-approved treatment options, a terminally ill, mentally competent adult patient's informed access to potentially life-saving investigational new drugs determined by the FDA after Phase I trials to be sufficiently safe for expanded human trials warrants protection under the Due Process Clause.

The prerogative asserted by the FDA — to prevent a terminally ill patient from using potentially life-saving medication to which those in Phase II clinical trials have access — thus impinges upon an individual liberty deeply rooted in our Nation's history and tradition of self-preservation. *See Glucksberg*, 521 U.S. at 721; *Flores*, 506 U.S. at 302. The district court never reached the question of whether the challenged FDA policy violates this protected liberty interest, and we therefore remand the case to the district court to determine whether the FDA's policy barring access to post-Phase I investigational new drugs by terminally ill patients is narrowly tailored to serve a compelling governmental interest.

Attachment C

Drug Czars

Editorial in the Wall Street Journal
By Steven Walker

May 7, 2007

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May 4, 2007

COMMENTARY

Drug Czars

By STEVEN WALKER
May 4, 2007; Page A15

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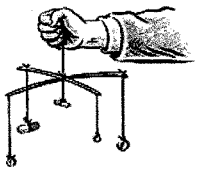
The Food and Drug Administration recently argued in the D.C. Court of Appeals that it has the power to ban meat and vegetables without violating anyone's fundamental rights. The agency chose this bizarre position in an attempt to counter arguments made by patients and their advocates in *Abigail Alliance v. von Eschenbach*. This groundbreaking case challenges the agency's refusal to grant access to investigational drugs, even as a last resort for terminally ill patients.

Last year, a three-judge panel decided that the FDA is violating the due- process rights of terminally ill patients by denying them access to promising investigational drugs. In response the FDA moved for a rehearing by the full court, hoping to prevent a lower court-supervised examination of whether its draconian policies actually serve a narrowly tailored compelling governmental interest. In layman's terms, this means the FDA would have to show its policies toward terminal patients are so critical to the well-being of society that they supersede (in broad and highly imperfect fashion) the fundamental right of an individual to pursue life free of undue government interference. The FDA knows their policies will not survive this test, and doesn't want the question asked.

Consider the FDA's handling of Genasense, a new drug for melanoma and chronic lymphocytic leukemia (CLL), two often terminal forms of cancer. The drug is being developed by Genta, a small, innovative company with only one approved drug and limited financial resources. Despite compelling evidence that Genasense is making progress in fighting both diseases, the FDA appears determined to kill the drug.



In the case of the melanoma application, instead of reviewing the clinical-trial data in accordance with usual methods (which showed positive results), the FDA chose a nonstandard statistical approach aimed at discrediting the results. The agency used this analysis in its briefing to its advisory committee, claiming that the drug might not be effective. The committee then relied on that information to vote against approval.

David Gothard

Now, Genta has found a serious mathematical error in the FDA's analysis, rendering its results meaningless. Genta is filing a complaint under the Federal Data Quality Act to correct the record. But in the meantime, the drug remains unapproved and melanoma patients continue to wait.

Genasense was also shown in a well-run, randomized clinical trial (the FDA's gold standard) to cause a complete disappearance of disease in 17% of patients with advanced CLL when combined with two older drugs. Just 7% of patients in a control group who received only the older drugs experienced similar benefit. The responders to Genasense have seen their relief last an average of 36 months, while those using other drugs saw their cancer return, on average, in 22 months.

Following these results, the Director of the FDA's cancer division, Dr. Richard Pazdur, again convened a public meeting of his advisory committee. After an agency presentation designed to elicit a negative outcome, the panel voted 7 to 3 against approval, triggering an immediate reaction of surprise and dismay among many CLL experts.

But the committee vote is less surprising if one knows that the FDA appointed several voting consultants to the committee (none of them CLL experts), and recused from the meeting the only sitting member of the committee who is an expert in CLL. Perhaps even more troubling, two of the voting committee members worked behind the scenes as undisclosed consultants for the FDA on Genasense, then without disclosure voted in the open meeting.

A shocked Genta quickly requested a meeting with the FDA to seek clarity on the agency's position, and to present additional information from patient follow-up. On the referral of an eminent leukemia expert, Genta asked if we would attend the meeting as witnesses in our capacity as patient advocates. No compensation was offered, requested or received.

Most of the meeting was consumed by getting the FDA to admit the obvious: The long-lasting, complete disappearance of CLL and its symptoms constituted "clinical benefit." Making these arguments were two cancer-medicine professors at M.D. Anderson Cancer Center, the recused ODAC member and an immediate past president of the American Society of Hematology -- all experts in CLL. None were employees of Genta and collectively represented a far more qualified advisory committee than the one that the FDA had convened.

The FDA's inane answer to the CLL experts was that the long-lasting disappearance of disease in patients taking Genasense was a "theoretical construct" and not grounds for approval.

The experts explained to the FDA that complete responses in advanced CLL patients are the medical equivalent of the Holy Grail. The FDA finally agreed, but was unimpressed with emerging data showing responders to Genasense living longer than responders in the control group.

The experts were unanimous in advising that Genasense should be approved, but the FDA was unmoved. The agency's Dr. Pazdur suggested that Genta could make the drug available as an unapproved treatment through an expanded access program -- this from a regulator fond of stating that the best way to get a drug to patients in need is through approval! In this case the agency was saying to Genta: We are not going to approve your drug, but any patient who needs it can have it so long as you give it away.

Genta responded that nonapproval would be a denial of patient access to Genasense because they could not afford to give it away in an expanded access program. Twice, Dr. Pazdur referred to that logic as a "business decision."

Less than 48 hours later, the FDA rejected Genasense. Within days Genta made a "business decision," laying off a third of its staff in a cost cutting move aimed at keeping the doors open long enough to appeal the FDA's decision. The appeal was filed in early April. Genta's announcement of the filing included a statement from one of the expert physicians: "It is puzzling that they would deny approval to a drug that met its primary and key secondary endpoint,

especially since these findings were observed in the only randomized controlled trial that has ever been conducted in patients with relapsed CLL."

The FDA's handling of Genasense lays bare the all too common, aggressive incompetence of the FDA's cancer-drug division and should lead to an immediate examination of its policies and leadership, followed by swift corrective action.

As for the FDA's belief that their power to control us and even deny us the pursuit of life itself is unlimited under the Constitution, we can only hope the appeals court disagrees. An agency that blocks progress against deadly diseases -- while arguing that its power to do so is above challenge -- is in dire need of a court supervised review.

Mr. Walker is co-founder and chief adviser for the Abigail Alliance for Better Access to Developmental Drugs. He receives no compensation for his work as an advocate, nor has he ever received compensation from any private or public-sector entity involved in drug development, approval or marketing.

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Attachment D

ODAC and the FDA, Arms-Length or Arm-In-Arm?

Slides from Presentation to the Oncologic Drugs Advisory Committee
by Steven Walker

September 6, 2006

Abigail Alliance
for Better Access to Developmental Drugs

Oncologic Drugs Advisory Committee
September 6, 2006

ODAC and the FDA
Arms-Length or Arm-In-Arm?

Oncologic Drugs Advisory Committee
September 6, 2006

Does the Office of Oncology Drug Products Have Too Much Control Over ODAC?

Is ODAC Too Close to the Office of Oncology Drug Products?

Oncologic Drugs Advisory Committee
September 6, 2006

How Are ODAC Members Selected and Who Selects Them?

ODAC Member Selection

- The Nomination Process - Transparent
- **The Screening Process - Murky**
- **The Selection Process - Opaque**

ODAC Member Selection

Final Selection – How It Is Done

- Nominations are Sent to the Division
- The Division Decides Who They Want
- And Who They Don't Want

Technical ODAC Members
Where Do They Come From?

Who Is "The Division?"

"The Division" is the Office of Oncology Drug Products

A Memorandum

Memorandum

Date:
To:
From: Richard Pazdur, M.D., Office Director
Office of Oncology Drug Products
Subject: Nomination for Oncologic Drugs Advisory Committee

Dear:

Thank you for your interest in the Oncologic Drugs Advisory Committee (ODAC) of the Food and Drug Administration, Center for Drug Evaluation, Office of Oncology Drug Products. After careful consideration, I am sorry to inform you that the vacancy for participation on this committee has been offered to, and accepted by another nominee.

The agency was very fortunate to receive a large number of extremely qualified and highly meritorious recommendations, you being among them. However, with such a varied and pioneering field of oncology, and after much deliberation, the candidates were chosen based not only on their qualifications but on the needs of the committee with consideration to issues and products inherent to the applications and processes of the agency.

Again, thank you for your interest in the ODAC.

Best,

Richard Pazdur, M.D.
Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration

The Division and ODAC

What Else Does the Division Control

- When to Convene the Committee
- The Subjects/Drugs to be Discussed
- Content/Spin of FDA Briefing Documents

The Division and ODAC

More Division Control

- Who Sits and Votes As Members
- Who Sits and Votes as Consultants
- What Questions are Posed for a Vote

The Law

Federal Advisory Committee Act (FACA)

- the advisory committee will not be inappropriately influenced by the appointing authority or by any special interest, but will instead be the result of the advisory committee's independent judgment;"

The Regulation

Title 21 Code of Federal Regulations Subchapter A - Part 14

- "An advisory committee is utilized to conduct public hearings on matters of importance that come before FDA..."
- Voting members serve as individuals and not as representatives of any group or organization which nominated them or with which they may be affiliated.
- Its membership is balanced fairly in terms of the points of view represented in light of the functions to be performed.
- It is constituted and utilizes procedures designed to assure that its advice and recommendations are the result of the advisory committee's independent judgment.

Clear Intent of the Law and Regulation

The Purpose of an FDA Advisory Committee is to Provide Balanced, Independent Advice In A Manner Open to the Public

An Important Question

Should the Office of Oncology Drug Products Control the Membership of ODAC?

Does This Practice Compromise the Independence Of ODAC?

An Important Question

Is ODAC Too Close to the Office of Oncology Drug Products?

Oncologic Drugs Advisory Committee
June 2, 2006

Last ODAC Meeting – More Evidence of Arm-in-Arm Relationship

Director's Comments Regarding Service of Departing Members

Dr. Silvana Martino, D.O., Chair
Dr. Bruce Cheson, M.D.
Dr. Gregory Reamon, M.D.

Oncologic Drugs Advisory Committee
June 2, 2006
Statement by Dr. Richard Pazdur

Regarding all three departing members:

"...we have really used them quite extensively, and they have developed I think very close working relationships with many at the FDA."

Oncologic Drugs Advisory Committee
June 2, 2006
Statement by Dr. Richard Pazdur

[Dr. Martino] "...has always been available to the FDA staff to provide consultations to us and to bounce off ideas in a very professional and positive manner."

Oncologic Drugs Advisory Committee
June 2, 2006
Statement by Dr. Richard Pazdur

Dr. Cheson .... "has provided to the Agency numerous consultations outside of the ODAC meetings on end of phase two meetings and official and unofficial consultations with the members of the staff."

Oncologic Drugs Advisory Committee
June 2, 2006
Statement by Dr. Richard Pazdur

[Dr. Reamon] ... "has been available, again like the other members of this committee, in helping us with end of phase two meetings, difficult questions that we have regarding exclusivity, and other pediatric issues that the Agency faces."

How Involved are ODAC Members with FDA

Questions That Deserve Answers

- Are members of ODAC working directly with FDA on regulatory strategies for specific INDs Outside the Public Meeting Process?
- Do ODAC members work with FDA on active INDs prior to scheduling of meetings on an NDA or BLA for those drugs?
- Do they assist with or attend end of Phase II meetings for specific drugs at the request of the FDA?
- Have any of the drugs they worked on with FDA been later brought before ODAC for its advice?

Potential Conflict of Interest 1

How Can a Committee Provide Balanced, Outside, Independent Advice to FDA If The Committee Roster and Agenda are Entirely Controlled by the FDA Staff Asking for That Advice

Potential Conflict of Interest 2

How Can any Member, or the Committee as a Whole, Provide Outside Independent Advice to FDA?

If Some or All of the Members Also Work Out of the Public View Directly With FDA to Set Agency Policy or Strategies Regarding INDs That May Eventually Come Before the Committee?

Procedural Problems

Deliberations of Advisory Committees Are by Law and Regulation to be Open to the Public

How Do Formal and Informal Consultations With FDA Staff by ODAC Members Outside the Public Meeting Process Meet This Standard?

The Law and Regulation Are Clear

The ODAC is Not Supposed to Be a Part of, An Extension of, or a Tool of the Office of Oncology Drug Products

ODAC Is Intended to Advise and Instruct the Office from a Vantage Point that is Clearly Outside and Independent of the FDA in a Manner Openly Visible to the Public

A Balanced, Independent, Public ODAC How Do We Get There?

- Remove Any and All Nomination and Selection Tasks for ODAC Members and Other Voting Members from the Office of Oncology Drug Products and Probably from CDER
- Require That All Nominations to ODAC Be a Matter of Public Record – Including Identification of Both the Nominating and Nominated Parties
- Limit All Interactions Between FDA and ODAC Committee Members to the Open Committee Meeting Process or to the Formal Assignment Process Specified by Regulation

A Balanced, Independent, Public ODAC How Do We Get There?

- End Non-Public ODAC Member Participation in FDA Internal Proceedings Regarding Active INDs, Such as End of Phase II Meetings
- Post All Pending Committee Vacancies No Less Than Six Months Prior to the Vacancy Opening Up on the FDA's Advisory Committee Web Page
- Make the Advisory Committee Member Selection Process and Duties More Transparent - Immediately Post the Necessary Information on the Agency's Web Site

An Independent ODAC Closing Thoughts

The Role of This Committee is to Provide Outside, Balanced, Independent Advice To FDA on Matters of Critical Importance to The Cancer Research, Clinical and Patient Community

The Member Selection Process, Administration and Utilization of Advisory Committees by FDA Should Be Reformed to Ensure that the Intended Balance, Independence and Transparency to the Public is Achieved

Abigail Alliance
for Better Access to Developmental Drugs

Working for Patients

Attachment E

Making FDA Work for Patients

By Steven Walker

Legal Backgrounder, Vol. 20, No. 10.
Washington Legal Foundation.

February 25, 2005

Legal Backgrounder

WLF Washington Legal Foundation
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2009 Massachusetts Avenue, NW
Washington, DC 20036
202.588.0302

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MAKING FDA WORK FOR PATIENTS

by

Steven Walker

As a nation, we are accustomed to scientific progress. The advances of the last century have, for example, allowed us to live years longer in better health, and brought us new medical treatments that can cure or control a variety of previously limiting or fatal diseases.

Now, during this period of unprecedented success, patients face a regulatory crisis of massive proportions. Our regulatory system has failed to evolve with the advancing science, leaving us with a drug development and approval process no longer capable of effectively protecting and promoting the public health. At the center of this crisis is the U.S. Food and Drug Administration (FDA).

A vast number of patients are being left out of medical progress — progress inhibited by a federal agency which tells dying patients that waiting, and dying while they wait, is in their best interests.

Background. In the 1970s, the United States made a national commitment to basic medical research and has steadily increased funding for those efforts through the present. Over the last 25 years, federal policy has also recognized the potential of the private sector to accelerate medical progress by utilizing its capital and efficient product development models to tackle the most difficult part of the process: transforming basic research discoveries into usable treatments. In the 1980s and 1990s, in an effort to boost industry and investor interest, Congress passed a series of laws creating incentives for private-sector investment in development of new and better treatments.

This focus on basic research and engaging the private sector is now paying off. New information regarding causes and possible treatments for a variety of serious diseases is emerging from our basic research laboratories into the hands of public- and private-sector organizations that can transform such knowledge into safe and effective new treatments.

In the meantime, the FDA has been relying on a drug development and approval model conceived decades ago. In the early 1960s, realizing that science does not always succeed, and that pharmaceutical companies and physicians are fallible, Congress modified the Food, Drug and Cosmetic Act to require the FDA to determine that new medicines are both safe *and* "effective." Until then, the FDA had long been regulating drug safety, but had no mandate to evaluate effectiveness.

At that time, biomedical knowledge and the technology needed to broaden it were crude by today's standards. Drug discovery proceeded largely by trial and error, screening thousands of compounds to find a few that worked in a lab, and perhaps one that eventually could serve as a viable treatment. Researchers were flying blind. The state of the art also limited the options available to the FDA, leaving the regulators with no choice but to devise equally primitive methods for measuring effectiveness.

Steven Walker is Regulatory Advisor to the Abigail Alliance for Better Access to Developmental Drugs, an Arlington, Virginia-based patient group dedicated to helping cancer patients and others with life-threatening and serious diseases.

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The basic elements of our comparative clinical trials system are fourfold. Researchers first determine (using a small number of volunteers) an appropriate dose and whether the drug appears to be safe at that dose (i.e., substantially less dangerous than the condition it was intended to treat). Next, the drug is tested in a larger number of patients with the specified condition. It is then given to an even larger number of people with the condition and compared to a similar number of people with the same condition, called controls. Control group patients might receive nothing, a placebo (sugar pill), or an already-approved drug known to work at some level for the same condition. Finally, the outcomes for the two groups are compared and the results are used to evaluate whether the new drug is more effective than nothing, or at least is as effective as an older drug. If it is found to be acceptably safe and works at some level based on these standards, also called endpoints, the FDA may approve it.

The data produced from the clinical trials are well suited to evaluation using the mathematical tool of statistics, and FDA adopted the rules of statistics from the outset as the basic drivers for clinical trial design and analysis of trial results. The thinking was to structure the trials in such a way that the data produced would be amenable to statistical analysis and would meet its theoretical tests for validity. As the field of human clinical testing evolved, the trials were increasingly designed to facilitate the strengths and also the severe limitations of statistical analytical techniques. Simultaneously, the FDA established increasingly detailed and rigid standards governing approval decisions for new treatments. These standards were largely statistical in nature, hinging on artificial measures of data validity called "probability values" and "confidence limits." Another requirement of the statistical approach was the need to compare "apples to apples" in the clinical trials, resulting in the parsing of a single disease (*e.g.*, colon cancer) into many disease sub-types for which an isolated approval could be obtained.

On the positive side, this approach did not require the FDA to know for certain what caused the disease being treated or what the new drug was doing to treat it. In other words, it enabled the FDA to be "science-blind." In a time when those things were often unknowable, a phased clinical trials system would still allow the FDA to achieve its mission of protecting and promoting the public health. Another plus for regulators was that because the statistical approach did not require any detailed scientific knowledge or clinical skills, decision-making based on sound scientific and clinical judgment was not required or even allowed. The removal of these factors from the approval process relieved decision-makers at the FDA from any direct accountability for approving a drug that later proved to be unsafe, or for delaying approval of a new treatment that could have saved many lives.

On the negative side, the FDA's focus on fine points of statistical methodology in making approval decisions for new treatments caused the trials to be designed with restrictive entry criteria that excluded many patients from participation. Perhaps the most damaging effect of the focus on statistical methodology was that it often had the effect of banishing from the approval process consideration of the real science underlying the disease and the drug.

The science-blind approach to drug assessment has also fostered a risk-averse culture at the FDA, one strongly favoring the invisible mistake of delaying the approval of safe and effective treatments to minimize the chance of making a highly visible mistake — approving an unsafe or ineffective drug that must later be withdrawn. The way the FDA is organized has reinforced this risk aversion. It is an organizational structure where responsibility for decisions and performance is spread thin and wide across a number of disciplines and offices. This structure provides little incentive for any one reviewer to step outside his or her own chute of responsibility into the path of accountability. When mistakes happen, the agency invokes a rote defense — procedures and policies were followed, statistical standards were met, and therefore the mistake was unavoidable. No one individual is responsible because no one individual can be responsible.

The Effect. The process of moving new discoveries from the laboratory to the bedside is called "translation," and there is widespread agreement that we are failing to convert an unprecedented expansion of scientific knowledge into more effective treatments. There is considerably less agreement on why we are failing, mainly caused by a near cult-like belief in the purity of statistical methodology in the drug approval

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process. In this new age of "smart science" drug invention, we are haltingly laboring ahead with a decades-old science-blind translation system.

The FDA has worked diligently to preserve and entrench its primitive methods, even as the field it regulates surpasses it. Had the FDA kept pace, we would now be evaluating and approving some new drugs and treatments based on our knowledge of the causes of disease, and direct observation of how a new drug affects the cause. We would be using science-based facts obtained from direct observation with small, scientifically-driven clinical trials designed to confirm reasonable safety and effectiveness rather than to establish it, and we would follow up after approval of a new treatment with long-term monitoring in actual patient populations.

Unfortunately, the FDA claims to have no idea how to do this and has begun well-intentioned but unfunded initiatives called "Critical Path" and "Stimulating Innovation" to try to figure it out. In typical fashion, the agency has reviewed its practices and the field in general, and concluded that most of the problems lie beyond its walls. Until the FDA realizes that the organizations outside the FDA are simply responding to its mandates, sponsors trying to translate discoveries to patients will have to make do with the FDA's science-blind approach.

The Patients. As the FDA continues to stand still, encumbered with a bureaucratic resistance to change, it remains a drag on medical progress and a lethal barrier to a vast number of terminally-ill Americans trying to gain access to that progress. Those patients invariably find themselves fighting two adversaries: their life-threatening disease and the FDA's "process before patients" system in which serving the best interests of patients is secondary to the FDA's inflexible policies and practices.

Every year more than one-half million Americans die in the U.S from cancer alone. As recently as ten years ago, there was little to be done. The pipeline of new cancer drugs showing evidence of effectiveness was sparsely filled. The focus of most clinical trials was to find new ways to use a small number of existing drugs already known to be inadequate, and progress was being made in rare, tiny steps. According to experts, cures were many decades away.

By the mid-1990s, however, a first wave of knowledge-based, smart science cancer drugs were entering the FDA's clinical trials process, with many more in pre-clinical development. That number has now grown to several hundred highly-innovative investigational treatments in clinical trials today. The new drugs are variable in their genesis and design, reflecting the diverse nature of scientific advances. In cancer, they consist of small chemicals designed to block receptors on cancer cells, manufactured biological antibodies designed to gum up cancer cell signaling mechanisms, and even biological molecules attached to small radioactive particles that are injected into the bloodstream where they seek out cancer cells and deliver the radiation directly to the tumors. Some show startling evidence of safety and effectiveness in early testing, but take years to reach patients as they travel the tortuous path of the FDA's outmoded drug development and approval system.

One of these new creations, and its path to patients, provides a telling example of the problem. A drug called STI-571 (now known as Gleevec) worked so well for patients in a small Phase I trial, many labeled it a new miracle cancer drug. In 1998, all 31 patients in the trial experienced dramatic positive responses to the drug without any serious side-effects. Tragically, instead of being delivered immediately to patients with a highly-lethal form of leukemia, the FDA required a Phase II trial as a matter of pro-forma policy before the drug could be made available to anyone outside a clinical trial. Some patients eventually got the drug before it was approved based on data collected in the Phase II trial and a program known as "compassionate use." Many patients, however, died waiting for the FDA to approve Gleevec; an approval that didn't come for more than two years after its safety and efficacy were well established. It has since proven to be effective in treating at least one additional form of lethal cancer, and other life-saving and life-extending uses for the drug appear likely to emerge.

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Thanks to the ineffectiveness of FDA policies governing clinical trials and approval standards, the Gleevec scenario has repeated itself numerous times in the last seven years where drugs have been discovered to be safe and effective against a variety of deadly cancers shown in early and even late-stage clinical trials. The FDA's staunch resistance to change has led to slowed and even stalled progress against cancer and other deadly diseases, and a mounting toll of shortened lives that may now number in the millions.

Despite the obvious and increasing collision between scientific progress and the FDA's failure to keep up, the agency has yet to implement a single change resulting in direct benefit to patients, opting instead to begin studies and initiatives that will take years to yield results. In the meantime, its forty-year-old assessment process remains in place, and a vast number of patients die every year waiting for medical progress already made to reach them.

The recently reported safety problems with pediatric anti-depressant drugs and with the pain reliever Vioxx arose from the same fundamental shortcomings that cause the FDA to routinely delay approvals for breakthrough cancer treatments.

Simply put, statistics is a set of powerful mathematical tools scientists use to help them test or understand data from their experiments, but statistics are almost never used as the *only* basis for making decisions. Statistical methods alone give a limited view of scientific data when they lack an understanding of the underlying scientific phenomena. Yet the FDA has built its entire system of drug development and approval around just that approach. The result is an FDA operating with outdated, ineffective regulations and policies that drive up the cost of medical progress and prevent the delivery of that progress to those who need it most: patients suffering from serious and terminal diseases. The agency needs new decision-making tools and approval authorities that are based on real science, not just statistical measures like "p-values" and "confidence limits." If you don't know what a p-value or confidence limit is, you just might be better at recognizing and approving new breakthrough cancer drugs than the FDA, saving a lot of lives as a result.

Possible Solutions. The Abigail Alliance for Better Access to Developmental Drugs and its counsel, the Washington Legal Foundation, have proposed a regulatory reform called "Tier 1 Initial Approval." It is designed to make promising new treatments available to terminally-ill patients in a time frame meaningful to them — that is, while they are still alive. The program would allow drug sponsors to sell an investigational drug (a drug undergoing clinical trials in humans) to patients with life-threatening illnesses who have not been able to gain entry into a clinical trial. Those patients would thus have an opportunity to take the same risks, and seek the same potential benefits, as patients in the clinical trials. Tier 1 is a comprehensive proposal intended to improve patient access to medical progress while protecting the clinical trials system, providing incentives for sponsor participation, and creating a potential for insurance coverage and patient assistance programs to cover the cost of Tier 1 drugs for patients reasonably choosing to pursue better, longer lives. A petition asking for adoption of the new authority was submitted to the FDA on June 11, 2003. The petition shows in detail that such a program is within the FDA's statutory authority and does not require new legislation.

On July 28, 2003, the Abigail Alliance and the Washington Legal Foundation filed a lawsuit in federal court against the FDA and its parent agency, the U.S. Department of Health and Human Services, asking for a ruling that the FDA's policies violate the constitutional rights of terminally ill patients with no approved treatment options by depriving them of life and liberty without due process and by infringing on their right to privacy. The U.S. District Court for the District of Columbia rejected these constitutional arguments in an August 30, 2004 ruling, and the case is now on appeal.

Ultimately, the remedy for overcoming the regulatory barriers between promising new medicines and the dying patients who desire them rests with a cultural change within FDA: a perspective in which the agency considers itself at fault when it makes a mistake in delaying an important new medicine no less than when it makes a mistake in approving a new medicine. How to bring this cultural shift about is the major challenge facing lawmakers and agency leaders.

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Attachment F

Decelerated Approval

Presentation to the Oncologic Drugs Advisory Committee
By Steven Walker

November 8, 2005

Presentation to the Oncologic Drugs Advisory Committee
November 8, 2005

By

Steven Walker
Abigail Alliance for Better Access to Developmental Drugs

Decelerated Approval

My name is Steven Walker. I am Chief Advisor to the Abigail Alliance for Better Access to Developmental Drugs. I am a volunteer and receive no compensation of any kind for my efforts as a patient advocate or for my work on behalf of the Abigail Alliance. I am paying my own expenses to be here today, and I have no financial relationships with drug companies or any other entity or organization directly involved in the development, approval or sale of medical treatments.

Slide 1

The FDA's Decelerated Approval Initiative for New Cancer Drugs

I suspect many of you were here for the first ODAC meeting on this subject in March 2003. Frank Burroughs, President of the Abigail Alliance, and I were here as well, and we spoke at that meeting asking that the FDA not proceed with the policies they were clearly about to launch. In my opinion, the FDA wasn't really looking for ODAC's advice on its plans, but rather used the meeting as a platform to roll out what can only be described as a decelerated approval initiative.

The FDA also should have known - and in fact it is hard to believe that they did not know - that its decelerated approval initiative would be devastating for terminally ill cancer patients whose only hope was gaining access to medical progress while still alive.

Despite the stark truth of what the FDA's new policies would do in slowing translation of new therapies to the clinic and the patients that needed them to live, the FDA forged ahead – rolling out its plans to turn accelerated approval and Phase IV clinical trials into a high risk minefield for sponsors. In fact, on that day in March 2003, the FDA effectively eliminated the accelerated approval pathway as a viable mechanism - the exact opposite of what the FDA should have been doing in this time of accelerating scientific progress against cancer.

I would now like to take you through the start and evolution of the FDA's decelerated approval initiative. I am going to read to you some of the statements made by FDA in ODAC meetings to launch the decelerated approval initiative, then talk about a couple of

examples that illustrate the effect those policies have had on the effectiveness and ethics of our clinical trials and translation system.

At the start of the March 12, 2003 meeting, Dr. Richard Pazdur concisely outlined the FDA's new policies regarding accelerated approval. Dr. Pazdur opened with the following comment:

Slide 2

"Accelerated approvals have been granted with the trial design using single arm trials in refractory populations as stated previously. These trials obviously allow more rapid trial completion and hence expedite drugs to patients with life-threatening diseases."

This statement seems to demonstrate the FDA awareness that approving drugs based Phase II single-arm trial data could deliver progress to patients quickly – the central mission of the accelerated approval concept. However, the next comment went in a different direction:

Slide 3

"An alternative trial design uses a randomized trial allowing accelerated approval on the basis of an interim analysis of surrogate endpoints, for example, response rate or time to progression."

Anyone who has been following the FDA's policies for cancer drugs knows that this was not an idle comment. It was the first in a new set of policies, in effect a new rule, that would be broadly enforced by FDA oncology reviewers.

Slide 4

Next Dr. Pazdur stated that:

"Randomized trials also may optimize the evaluation of novel cytostatic agents by allowing an assessment of slowing or retarding or preventing tumor progression. This may simply not be possible with single arm trials."

We now know this meant that the prospects for approval of new cancer drugs based on single-arm trials were not good.

Slide 5

Moving further into the new rule book, Dr. Pazdur said:

"Obviously randomized trials are more expensive than single arm trials and take more time. "

Demonstrating that FDA was aware the new rules would slow translation and increase the costs of that translation for new safe and effective cancer drugs.

Slide 6

Moving on he stated:

"Survival analysis can be complicated and confounded by cross over and subsequent therapy."

And sponsors soon found they had little choice but to design and conduct increasingly unethical randomized, double-blind, placebo-controlled clinical trials in refractory patient populations to stay within the "unmet need" requirement for accelerated approval.

Slide 7

Dr. Pazdur then made it clear how this was going to work in the context of Phase IV trials:

"The mandatory confirmatory trials to demonstrate clinical benefits are equally important as the initial trials demonstrating an effect on a surrogate endpoint leading to that drugs approval."

FDA was making it clear that the post-approval trials Congress said "may" be required by FDA, will in fact be required every single time. FDA was also making it clear that conduct and completion of those trials will be mandatory every single time, and that failure to comply could result in withdrawal of the drug, notwithstanding an inability to enroll the trial because it was unethical, obsolete or simply impracticable.

Slide 8

Then we heard how Decelerated Approval would fit in to FDA's new policy paradigm:

"Hence confirmatory trials must be an inherent and integral part of a comprehensive drug development plan and drug development strategy. "

It meant – do you want your drug approved or not? If you do, then follow the rules.

Although not obvious at the time, it also meant that that FDA would start delaying accelerated approvals until unethical, unnecessary double-blind, randomized, placebo-controlled, and in some cases no cross over Phase III clinical trials could be started, enrolled, and run to an interim analysis point.

Slide 9

In fact, the decelerated approval initiative effectively eliminated the accelerated approval pathway as a reasonable option for sponsors to pursue, moving the clinical trial requirements so close to those needed for regular approval that its intent – acceleration – was neutralized.

Punitive Drug Development and Approval

Slide 10

So what did we get from all of this?

A punitive enforcement program for Phase IV clinical trials and the potential for withdrawal of safe and effective cancer drugs based on any failure to complete the Phase IV trials, or to unequivocally achieve regular approval endpoints.

Slide 11

Accelerated Approval would be available only for sponsors whose development program had already achieved substantial compliance with endpoints intended for regular (full) approval.

Slide 12

Accelerated Approvals would be denied or delayed to ensure a large, desperate pool of patients facing death from their disease to coerce patients under duress to enroll in marginally and even clearly unethical Phase III clinical trials, thus resolving the Phase IV trial enrollment issues.

Slide 13

The Decelerated Approval initiative is in direct conflict with the intent of Congress – the idea to speed up delivery of medical progress to patients who need it to live.

The initiative was conceived and implemented unilaterally by FDA staff over the protests of some stakeholders including the Abigail Alliance.

The policy shifts happened in plain view of agency leadership who cannot legitimately claim they did not understand the implications, because we told them - repeatedly.

And most tragically – many thousands of patients died prematurely, waiting for drugs and medical progress that should have been instead quickly delivered to the clinics.

Slide 14

A compelling example of the effect the Decelerated Approval Initiative has had on medical progress and patients is what happened with Bayer's Bay 43-9006, now known as Sorafenib.

Coming out of Phase II in 2003, Sorafenib certainly appeared to be the kind of drug that Congress intended would be eligible for Accelerated Approval – but no Accelerated Approval application was submitted.

Of course we can only speculate why, but I think we can speculate accurately that Bayer received the message that Accelerated Approval was off the table without a randomized trial.

We do know that Bayer negotiated a Special Protocol Assessment with FDA for a Phase III clinical trial. Perhaps finding themselves unable to predict what FDA was up to, they thought that course the only way to exert some control over the future handling of their drug by FDA.

Slide 15

The SPA negotiations produced an astoundingly unethical randomized, double-blind, placebo-only controlled, no cross over trial. The result of course, was patients on placebos dying prematurely inside the trial, and patients dying prematurely outside the trial because they couldn't get the drug by any means.

Earlier this year, after an interim review showed that Sorafenib was far better than a placebo, a result that should have been confidently expected by all concerned, Bayer came under intense pressure to allow cross over for the placebo patients who were still alive. A few months later Bayer started an expanded access program, but the delay of nearly two years in making the drug available denied thousands of renal cell cancer patients access to the Sorafenib, and many of them died, waiting.

While this is an especially egregious example, it is far from isolated.

Sorafenib remains unapproved.

Slide 16

Fast Forward to the ODAC meeting for Revlimid held on September 14, 2005. More than two and half years after the rollout, the devastating effects of the Decelerated Approval Initiative are on full display.

Revlimid is before the committee with compelling data from two Phase II single-arm trials. Celgene is asking for regular approval in the treatment of a targeted patient population with myelodysplastic syndrome, or MDS.

Slide 17

Dr. Richard Pazdur explains FDA's advice to Celgene for before they started the single-arm trial:

"On several occasions, as will be mentioned by the FDA reviewer, we have recommended to the sponsor before they began the study, that we look at randomized studies of this drug in MDS to have a better understanding of the disease in relationship either to other therapies or the natural history of the disease."

Despite the fact that the data is extremely compelling, FDA appears disappointed that a randomized trial was not conducted.

Slide 18

Fortunately Celgene kept its own counsel and proceeded with a single-arm, highly ethical trial in a targeted population based on earlier Phase II data. The Phase II trial proved undeniable efficacy in that targeted population.

Slide 19

ODAC agreed with Celgene that the drug should receive regular approval and that the proposed risk management plan for the drug is adequate.

Slide 20

But FDA seems unsatisfied with the Phase II trials and Dr. Pazdur reminds the ODAC that:

"I want to bring people back to the kind of regulations, and there is a mantra, adequate and well-controlled trials, adequate and well-controlled trials, adequate and well-controlled trials. I am mentioning that three times, because I think that is at the heart of the question here."

Just whose mantra is this and why does it have to be repeated three times? It seems the FDA is saying that safe and effective drugs should not be approved because the conditions of the mantra have not been met? There has been no randomized trial.

Slide 21

And then comes a revealing and we think critical exchange between a member of ODAC and a physician presenting for Celgene. Dr. Hussain of ODAC referring to the randomized trial requested by FDA asked:

"And why you chose not to do a Phase III trial when you were asked to do that?"

Slide 22

Celgene replied:

"We are going to go to Phase III. We are going to be doing a placebo-controlled trial. I have to say that in discussing that trial with the investigators, there is actually reluctance to put patients on placebo for very long based on the benefit that has been seen here."

Slide 23

"The patients who receive placebo, receive that for 4 months. If they are not responding, and we think that essentially, none of them are likely to respond from what we know, then, they will have the opportunity to go on to lenalidomide and continue on that as long as that seems to be benefiting them."

Slide 24

On October 3, 2005 only a few days before the FDA's deadline for a decision on Revlimid, FDA decided to extend its review time for a decision on Revlimid, citing new information submitted for the risk management plan – the same risk management plan that was provided to ODAC and judged to be adequate.

Slide 25

This exchange turned the relationship and missions of the FDA and the sponsors up side down. The sponsor was looking out for patients and the FDA was attempting to force conduct of an unethical, placebo-controlled trial for a drug that had already clearly shown compelling efficacy in a refractory, terminal patient population.

Just who is protecting who? Isn't it the FDA's job to protect the public from unethical and unnecessary human clinical testing?

Slide 26

We have a problem. The Decelerated Approval Initiative has been a misguided, devastating and extreme case of form over substance. In this case the substance shoved into the background was life itself for far too many patients, and stalled progress against cancer in a time when we should have been speeding up and learning new ways to accomplish translation more effectively.

Slide 27

We need to deactivate Decelerated Approval, banish inflexible mantras from the FDA's lexicon and get on with ways of improving and speeding up our translation of medical progress to patients.

Doing this will require change, and it also may require overcoming resistance to that change, which is why we have advisory committees, why FDA has an appointed commissioner, and why Congress has oversight authority. We call upon this advisory committee today, and on Acting Commissioner Von Eschenbach and Congress, to act on an expedited basis to make sure Accelerated Approval is reinstated, reactivated and improved. Right now, today, is the time for ODAC to get back to its original purpose. You are not here to support FDA's whims and wanderings – you are here to serve the best interests of patients – and if you don't believe that, you shouldn't be here at all.

Mr. PALLONE. Thank you. Dr. Gorman.

STATEMENT OF RICHARD GORMAN, M.D., CHAIR, AAP SECTION ON CLINICAL PHARMACOLOGY AND THERAPEUTICS, AMERICAN ACADEMY OF PEDIATRICS

Dr. GORMAN. Thank you, Mr. Chairman and members of the committee. I am Dr. Richard Gorman, a practicing pediatrician who has taken care of infants, children and adolescents for over 25 years. On behalf of the American Academy of Pediatrics, I would like to thank the subcommittee for holding this legislative hearing and for considering bills necessary to address the need for safe and effective drugs and medical devices for children.

The American Academy of Pediatrics urges the committee to reauthorize BPCA and PREA with necessary improvements, and to pass the new pediatric medical devices legislation to begin to close the gap between medical devices that children need and the devices that are available. I would like to thank Representatives Edward Markey and Mike Rogers for championing the pediatric medical device legislation, and express our continuing gratitude to Representative Anna Eshoo for leading the efforts on BPCA and PREA. Thank you, Mr. Chairman, as well as Chairman Dingell, for addressing these bills along with the user fees and drug safety legislation.

In previous testimony before this committee, I have credited BPCA and PREA with giving healthcare providers and families a great increase in the useful information on medicine for children. The American Academy of Pediatrics strongly supports the Improving Pharmaceuticals for Children Act of 2007, H.R. 2589, introduced by Representative Eshoo. We thank the committee for including much of H.R. 2589 in draft legislation we are considering here today. H.R. 2589 not only reauthorizes BPCA and PREA, but makes several needed changes to ensure their continued success. The reauthorizing legislation under consideration does four major things: it increases the dissemination and tracking of pediatric drug information; it integrates and strengthens BPCA and PREA's administrative process by affirming and institutionalizing an internal review committee that has already been created by the FDA to provide guidance and oversight for the FDA review divisons when issuing written requests under BPCA and pediatric plans under PREA. This legislation also expands the study of off-patent drugs by expanding the role of the NICHD to include studies of gaps in pediatric therapeutics, and it makes PREA a permanent part of the Food and Drug Act, and continues to give Congress the opportunity to regularly reevaluate the BPCA's incentives.

As I have testified in the past, the AAP evaluates proposed changes to BPCA's exclusivity incentive by asking two questions: would these proposals reduce the number of pediatric studies, and would these proposals be administratively burdensome to the FDA? The blockbuster proposal contained in the Committee Print is troubling, in that it does not protect against a potential reduction in pediatric studies and leaves open the question of whether regulations would be administratively burdensome. The AAP is on record for supporting the compromise crafted by Senator Chris Dodd in

Senate bill 1082. We urge the committee to retain this approach to adjusting the market exclusivity incentive.

The Pediatric Medical Device Safety and Improvement Act of 2007 will help children get the safe medical and surgical devices they need by strengthening safety requirements and encouraging research, development and the manufacture of pediatric devices. This bill, included in the committee print, strikes the right balance between new incentives and increased post-market surveillance, and puts forward a comprehensive package that serves as a critical step forward for children. The pediatric device legislation will help define the need for pediatric devices by better organizing the Federal response. It will create a device development mechanism of nonprofit consortia that will facilitate pediatric device development and manufacture through mentorship from experienced companies. It improves the humanitarian device exemption by eliminating the profit restriction for pediatric HDEs, which will increase the incentive for small companies to enter the pediatric device market and allow others to make a reasonable return. It makes needed improvements in the way the Food and Drug Administration tracks pediatric devices, and it strengthens post-marketing safety.

As recommended by the Institute of Medicine, this bill grants the FDA increased authority to ensure that approved medical devices are safe for children. Under this proposed law, the FDA would be able to require post-market pediatric studies as a condition of approval or clearance of certain devices. This legislation also allows the FDA to require a study of greater than 3 years, if necessary, to ensure that the study is long enough to capture the effect of a child's growth on the safety and efficacy of the medical device.

I would like to thank the committee for allowing me the opportunity to share with you the strong support of the American Academy of Pediatrics for the reauthorization of BPCA and PREA, as well as the new pediatric medical device legislation. We urge swift passage by this committee for the sake of all children. Thank you.

[The prepared statement of Dr. Gorman follows:]

American Academy of Pediatrics

TESTIMONY OF
RICHARD L. GORMAN, MD, FAAP
on behalf of the
AMERICAN ACADEMY OF PEDIATRICS

before the

COMMITTEE ON ENERGY AND COMMERCE
SUBCOMMITTEE ON HEALTH

UNITED STATES HOUSE OF REPRESENTATIVES

June 12, 2007

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Richard L. Gorman, MD, FAAP
Testimony before the Committee on Energy and Commerce, Subcommittee on Health
June 12, 2007

Mr. Chairman, members of the committee, I am Richard Gorman, MD, FAAP, a practicing pediatrician who has taken care of infants, children and adolescents for over 25 years. On behalf of the American Academy of Pediatrics, I would like to thank the subcommittee for holding this legislative hearing and for considering bills necessary to address the need for safe and effective drugs and medical devices for children.

I am here today on behalf of the AAP to urge the committee to reauthorize the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) with necessary improvements, and to pass new pediatric medical devices legislation to begin to close the gap between the medical devices that children need and the devices that are available.

I would like to thank Representatives Edward Markey and Mike Rogers for championing the pediatric medical devices legislation and express our continuing gratitude to Representative Anna Eshoo for leading the effort on BPCA and PREA. Thank you, Mr. Chairman, as well as Chairman Dingell, for addressing these bills along with the user fees and drug safety legislation.

In previous testimony before this committee, I have credited BPCA and PREA with giving healthcare providers and families with more useful information on medicines for children than we had in the previous seventy years.

PREA provides FDA with the authority to require pediatric studies of drugs when their use for children would be the same as in adults. BPCA provides a voluntary incentive to drug manufacturers of an additional six months of marketing exclusivity for conducting pediatric studies of drugs that the FDA determines may be useful to children.

REAUTHORIZATION OF BPCA AND PREA

The American Academy of Pediatrics strongly supports the Improving Pharmaceuticals for Children Act of 2007 (H.R. 2589), introduced by Representative Eshoo. We thank the committee for including much of H.R. 2589 in the draft legislation we are considering here today. H.R. 2589 not only reauthorizes BPCA and PREA, but makes several needed changes to ensure their continued success. This legislation:

Increases the dissemination, transparency, and tracking of pediatric drug information. Dissemination of pediatric information to families and healthcare providers must be increased in both BPCA and PREA. If families choose to involve their children in a clinical trial for a drug, then the drug label should reflect that study. The Government Accountability Office (GAO) found that about 87% of drugs granted exclusivity under BPCA had important label changes.[1] This is good news, but it is our view that every drug label should reflect when a pediatric study

[1] GAO 2007; 16

was done (either through BPCA or PREA) and the results of the study, whether the results are positive, negative, or inconclusive.

Moreover, FDA and drug sponsors must do more to communicate these label changes to pediatric clinicians. FDA should continue and expand its periodic monitoring of adverse events for both PREA and BPCA as this has been a useful tool to evaluate drug therapies after approval. Both H.R. 2589 and the committee print circulated by this committee improve the dissemination of pediatric drug information.

The transparency of the written request process used by FDA can be improved. Increased transparency will be beneficial to pediatricians, sponsors, and families. AAP recommends, and the committee print adopts, a provision requiring that written requests be made public at the time FDA awards exclusivity and that each written request be allowed to include both off-label and on-label uses.

We recognize that FDA has improved the written requests for pediatric studies since the incentive was first made law in 1997 and we recommend that the Institute of Medicine be engaged to review a representative sample of all written requests and pediatric assessments under PREA. This scientific review will provide recommendations to FDA to continue to improve the consistency and uniformity of pediatric studies across all review divisions within the FDA's Center for Drug Evaluation and Research. Representative Eshoo's bill and the committee print include this important provision.

Information regarding the number of written requests issued, as well as information regarding pediatric studies and label changes made as a result of BPCA is tracked and posted at FDA's website. This information is key to understanding the operation of the law for children and we are pleased that the legislation we are discussing today requires FDA to track this information for PREA and make such information available.

Integrates and strengthens BPCA and PREA administrative processes. In general, BPCA and PREA processes are working well at FDA, but more often as parallel programs than one administratively integrated pediatric study program. AAP supports, and these bills provide for the expansion of the existing internal FDA pediatric committee to include additional kinds of expertise within the agency and an integrated approach to the review and tracking of all pediatric studies requested or required by FDA, including the ability to require labeling changes.

Expands study of off-patent drugs. BPCA and PREA work well for new drugs and other on-patent drugs for which increased market exclusivity provides an appropriate incentive. However, for generic or off-patent drugs, BPCA and PREA have had a less effective reach.

In the last BPCA reauthorization, Congress tasked the National Institute for Child Health and Human Development (NICHD) with creating a list of off-patent drugs needing further study in children and with conducting those needed studies. Although Congress never appropriated any funding to NICHD for this purpose, NICHD nevertheless has made significant progress identifying important off-patent drugs in need of study and starting clinical trials on these drugs.

This legislation expands the role of NICHD in the current reauthorization to include study of the gaps in pediatric therapeutics in addition to generic or off-patent drugs. It also strengthens PREA so that needed pediatric studies can be conducted while drugs remain on patent.

BPCA also contains a mechanism through which pediatric studies of on-patent drugs declined by the sponsor can be referred to the Foundation for the National Institutes of Health (FNIH). FNIH is given authority to collect donations from pharmaceutical companies to fund such studies. Unfortunately, these donations were not forthcoming, and, as reported in the GAO report, no studies have been completed using this mechanism.

H.R. 2589 retains the legal authority of FNIH to maintain an emphasis on children and raise money from drug companies for important pediatric needs, such as training pediatric clinical investigators, building pediatric research networks, and studying pediatric disease mechanisms. However, it also wisely recognizes that the mandate to conduct pediatric studies of on-patent drugs should be discontinued. We urge the committee to reflect this change in the committee print and adopt this change to the law.

Makes PREA a permanent part of the Food and Drug Act and continues to reevaluate BPCA. We wish to express our sincerest gratitude to Representative Eshoo and the committee for agreeing that children deserve the same permanent standard of safety and effectiveness as adults. Both pieces of legislation would make PREA a permanent part of the Food, Drug, and Cosmetic Act. Congress need not debate every few years whether it should continue to require safety and efficacy information on drugs used in children.

It is useful, however, to reevaluate the exclusivity program periodically to ensure that the incentive offered achieves its desired goal despite changes in the dynamic pharmaceuticals market. This legislation would give Congress the opportunity every 5 years to analyze whether BPCA continues to strike the right balance between achieving critical pediatric information and providing an appropriate incentive to maintain the number and quality of pediatric studies for on-patent medication.

Maintain quality and number of pediatric studies while addressing "blockbusters." Providing drug companies 6 months of additional marketing exclusivity has been enormously successful in creating pediatric studies. Recent data shows that for the large majority of drugs, the return to companies for responding to a written request has not been excessive.

The Journal of the American Medical Association published a study in February that showed the return to companies for performing pediatric studies varies widely.[2] Most companies who utilize BPCA made only a modest return on their investment in children.[3] However, for the about 1 out of 5 companies with annual sales greater than $1 billion, the returns garnered through exclusivity have been very generous.

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[2] Li JS, Eisenstein EL, Grabowski HG, et al. Economic Return of Clinical Trials Performed Under the Pediatric Exclusivity Program. *JAMA*. 2007;297:490-488

[3] The median annual sales of a drug receiving pediatric exclusivity were $180 million with a return on investment of 1.5 times the cost of the study.

Concerns regarding the returns to these "blockbuster" drugs have been voiced by several Members of Congress and a number of proposals have surfaced to limit or change the market exclusivity extension, including the proposal for mandatory rulemaking to limit the incentive contained in the committee print.

Any proposal to amend the pediatric exclusivity provision must not reduce the quality and number of pediatric studies. The Academy reviews any proposal for limiting the exclusivity awarded under BPCA using two criteria: first, any change must not reduce the number of drugs studied in children. Any proposal that will decrease the number of companies responding favorably to a written request from FDA would undermine the essential goal of BPCA.

The second criterion is administrative simplicity. Proposals for using complicated formulas are likely to bog down the administration of the program by FDA and give rise to endless disputes between sponsors and the agency—including litigation. We cannot risk deterring or delaying important information getting into the hands of families and their health care providers. Every additional variable that Congress gives FDA to evaluate, when considering awarding the incentive, adds an additional level of complexity and moves FDA further from its core regulatory expertise.

The blockbuster proposal contained in the committee print is troubling in that is does not protect against potential reductions in pediatric studies and leaves open the question of whether the new regulation would be administratively simple. AAP is on record supporting the compromise crafted by Senator Chris Dodd in S. 1082. We urge the committee to retain this approach to adjusting the market exclusivity incentive. Moreover, the Congressional Budget Office notes that the Senate approach would reduce the cost of BPCA to the federal government by $50 million.

PEDIATRIC MEDICAL DEVICE LEGISLATION

The Pediatric Medical Device Safety and Improvement Act of 2007, H.R. 1494, will help children get the safe medical and surgical devices they need by strengthening safety requirements and encouraging research, development, and manufacture of pediatric devices. This bill, included in the committee print circulated by the committee, strikes the right balance between new incentives and increased postmarket surveillance and puts forward a comprehensive package that serves a critical step forward for children. H.R. 1494:

Defines the need for pediatric devices. The bill streamlines federal agency processes by creating a "contact point" at the National Institutes of Health (NIH) and requires FDA, NIH, and the Agency for Health Research and Quality to work together on identifying important gaps in knowledge and improving pediatric medical device development.

Facilitates pediatric device development and manufacture through mentorship. The bill also establishes six-year demonstration grant(s) to support nonprofit consortia to provide critically needed support in helping innovators with pediatric device ideas to navigate "the

system" successfully and bring new pediatric devices to market. The consortia will match inventors with appropriate manufacturing partners, provide mentoring for pediatric device projects with assistance ranging from prototype design to marketing, and connect innovators with available federal resources. The consortia will also coordinate with the NIH "contact point" for pediatric device development and the FDA for facilitation of pediatric device approval.

Improves the Humanitarian Device Exemption (HDE). The Humanitarian Device Exemption (HDE) was meant to be a tool for approving devices intended for small populations (less than 4,000 patients), which often included children and those with rare conditions, but the profit restriction on HDE-approved devices limits the effectiveness of the provision by forcing device manufacturers to only recover their research and development costs. By eliminating the profit prohibition for children, the bill increases the incentive for companies to manufacture pediatric devices, especially small manufacturers who are likely to embrace an affordable pediatric device development pathway with definable regulatory requirements.

Tracks pediatric device approvals and streamlines device development. The bill makes needed improvements in the way FDA tracks the number and type of devices approved for use in children or for conditions that occur in children. At present, FDA cannot satisfactorily produce data on the number and type of devices marketed for pediatric uses. The bill requires FDA to track new devices granted premarket approval or approved under the humanitarian devices exemption and report on the number of pediatric devices approved in each category.

Strengthens postmarket safety. The Institute of Medicine (IOM) studied post-market safety for pediatric medical devices for more than a year and produced a thorough report in 2005 entitled, "Safe Medical Devices for Children." The IOM found flaws in safety monitoring and recommended expanding the FDA's ability to require post-market studies of certain products and improving public access to information about post-market pediatric studies. The IOM reported:

> [T]he committee must conclude that FDA has lacked effective procedures to monitor the fulfillment of postmarket study commitments. The agency has lacked a basic, searchable listing of devices for which further studies were specified as a condition of their approval for marketing. Furthermore, it has not maintained any system for systematically monitoring the status of these study commitments based on periodic reports or updates from either its own staff or sponsors.[4]
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> FDA can ask for clinical studies prior to clearing devices, although clinical data are submitted for only a small percentage of devices that go through clearance. FDA cannot, however, order postmarket studies as a condition for clearance. It can (but rarely does) order studies subsequent to clearance through its Section 522 authority. Studies that are ordered subsequent to the approval or clearance of a device are limited to 3 years (which

[8] Field MJ and Tilson H. eds. Safe Medical Devices for Children, Committee on Postmarket Surveillance of Pediatric Medical Devices, Board on Health Sciences Policy; Institute of Medicine of the National Academies, 2005, p. 195.

often means a shorter period of evaluation for most individual study subjects). This may be too short a period for certain safety problems or developmental effects to be revealed.[5]

As recommended by the IOM, this bill grants the FDA increased authority to ensure that approved medical devices are safe for children. Under this law, the FDA would be able to require postmarket studies as a condition of approval or clearance for certain devices under section 522, if used frequently in children. This legislation also allows the FDA to require a study of greater than 3 years if necessary to ensure that the study is long enough to capture the effect of a child's growth on the safety and efficacy of a medical device. New post-market authority can address the currently limited amount of available data on devices for children and create a mechanism for ensuring that needed pediatric studies are conducted for a sufficient length of time.

I would like to thank the committee again for allowing me the opportunity to share with you the strong support of the American Academy of Pediatrics for reauthorization of BPCA and PREA as well as new pediatric medical devices legislation. We urge swift passage by this committee for the sake of all children throughout the United States.

I would be happy to answer any questions you may have.

Richard L. Gorman, MD, FAAP

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[9] IOM, p. 226.

Mr. PALLONE. Thank you, Dr. Gorman. We will start with questions and I will begin. I wanted to ask Mr. Guest, first, a couple of questions. The Consumers Union urges a zero conflict of interest policy for FDA advisory committee members. I have a couple of questions about that. How will this affect recruitment of advisory committee panelists? Will this hurt the level of expertise of the panels? Will we be setting up advisory committees with second-rate experts? You mentioned that CU does not believe the FDA has tried hard enough to find experts that are not conflicted. What makes you think this? I am just asking a bunch of questions. If you could try to answer them.

Mr. GUEST. I know that one group did a small survey. They called the deans of medical schools around the country and said, have people within your medical schools been asked by the FDA to be members of panels? And apparently the results were, in many cases, no. They said that there is not one person. There doesn't seem to be a concerted effort within the FDA to really do an extensive search for people that would be without bias, and that is a real concern at Consumers Union, and I mentioned that our Consumer Reports National Research Center did a survey; six out of 10 Americans do not believe that the FDA and Congress, in terms of laws, are doing enough. There is a real lack of confidence right now in the FDA. We know Consumer Reports is an exceedingly trusted organization, because people know we are absolutely free from bias of manufacturers. We don't take free advertising and don't take free samples and so forth. We think a similar kind of credibility, we would hope, a similar kind of creditability could be developed at the FDA and we think this legislation, the various parts of this legislation will help restore faith in the organization that we as consumers ought to depend on to protect us.

Mr. PALLONE. All right, let me go to my second question. This is about direct consumer advertising. One area of interest since the discussion drafts were released has been the 3-year waiting period on direct-to-consumer advertising and I keep stressing to everyone that this is not a moratorium. This is a case-by-case analysis in each. To some extent, I think it has been misrepresented as a 3-year moratorium, but it is actually case-by-case analysis. But the question keeps coming up about the constitutionality of the proposal in the draft, why do you think such a provision would be constitutional?

Mr. GUEST. Well, again, like the doctor from the FDA, I don't purport to be a constitutional expert on it, but I would suggest that the committee might consider having the Library of Congress, as a law division, maybe convene a group of constitutional scholars, who have no connection to special interests in this, to look at that question further. The reality is that every country but the U.S. and New Zealand actually prohibit direct-to-consumer advertising, because it is not, as members have said here earlier, it is not out there to try to educate consumers so they can make informed choices. It is out there to try to sell a product. And so there is great danger that direct-to-consumer advertising are not helping consumers. They are having the opposite effect. We actually did a survey, also, of doctors and said, how often do you feel pressured by consumers who come in, who saw these happy people living forever

after, and pushing for a drug? Well, the fact is, what you don't hear is that a lot of people who push these drugs are not living happily ever after. We have got some people in this room who can talk about that.

Mr. PALLONE. I know and you know, I appreciate your comments. I wanted to ask one more thing of Dr. Gorman before my time is up, but I just want to stress again that my concern is that if we just have a voluntary system with this advertising, that you have a bad actor and that essentially you have a bad actor who, even if the FDA determines that there are enough questions about a new drug to suggest that there be no advertising, that they don't have the power to stop it, other than the deceptive advertising, which is a separate issue, because something may not rise to the level of deceptive advertising, yet we have serious questions about it. And so I keep stressing this is not a moratorium. It is just a case-by-case analysis. But there has to be some stick at the end, otherwise you have a voluntary system and you don't get at the bad actor.

I just wanted to ask Dr. Gorman. You expressed concern with the way we adjust the exclusivity period for blockbuster drugs in our draft. Does the academy have any recommendations, other than the Senate proposal, which I know you said you support, that would achieve the goal of reducing the exclusivity period for blockbuster drugs, based on annual gross sales? We tried to come up with something that was a little different than the Senate. I know you don't like it, but do you have any other ideas other than the Senate, other than what is in the Senate proposal?

Dr. GORMAN. Before the beginning of this discussion, the academy set up those two criteria that would judge any proposal to limit exclusivity, which was that it would not reduce the number of studies, and two, it would be administratively simple for the FDA. And we didn't think that the committee markup language met those tests, so we felt unable to support them. But we would be willing to entertain other recommendations other than the one from the Senate bill, although we have supported that in public.

Mr. PALLONE. OK, thank you. Mr. Deal.

Mr. DEAL. I am going to have a question for everybody and I think maybe it will be a yes or no as you go down the line. Do you agree that the FDA should be responsible for approving all safety-related label changes for drugs? Dr. Loew, I will start with you.

Ms. LOEW. Yes, we do believe that FDA should have that authority.

Mr. GUEST. We are opposed to preemption. We think that the States ought to continue to have the authority that they have. The preemption provision that is in the FDA regulation has never been actually passed by Congress. That was something that the FDA put into the preamble of——

Mr. DEAL. Your answer is no?

Mr. GUEST. The answer is no.

Mr. DEAL. Mr. Ubl?

Mr. UBL. I will defer to the pharmaceutical side. But if I could amend your question and presume it applies to devices——

Mr. DEAL. Yes.

Mr. UBL. Well, we believe that FDA should have that sole authority.

Mr. DEAL. Dr. Zuckerman?

Ms. ZUCKERMAN. No.

Mr. WALKER. No.

Dr. GORMAN. Yes.

Mr. DEAL. Mr. Walker, your answer surprises me.

Mr. WALKER. In all honesty, sir, it is an issue that I don't have a full understanding of.

Mr. DEAL. Well, if we are going to allow labels on drug products to be amended because of safety concerns, who besides the FDA do you think ought to make that determination, trial lawyers in the lawsuits, in the States?

Mr. WALKER. Well, sir, it is a loaded question and the——

Mr. DEAL. Well, that is what I am up here for.

Mr. WALKER. Yes, sir. The reason it is a very loaded question is because the Abigail Alliance has a very, I guess, a very high lack of confidence in the FDA's ability to make good safety decisions. And the reason for that is that the FDA is an entirely statistical agency and the statistical tools that are used to determine, to essentially find the safety needle in the haystack, are weak. You are working with very dirty—now understand, I am a scientist. I am not a scientist in the medical field. I am a scientist in the environmental field, but I know a great deal about data. We think that the FDA needs a complete rebuild in the way it does its science. We think that the idea that we practice our medical science and all clinical research, limited by the very restrictive rules of statistics, has caused the FDA to be an institutionally incompetent agency, in terms of being able to determine and to balance risk versus benefit. It is not that the people are incompetent. It is that the tools they use aren't working.

Mr. DEAL. Well, unfortunately, we don't have within the realm of any of these pieces of legislation an effort to rebuild a new organization for purposes of determining patient safety.

Mr. WALKER. Actually, sir, you do. It is the Reagan-Udall Institute and it should be pumped up and put on steroids.

Mr. DEAL. Well, it is contained in one of the bills that we have here. Dr. Loew, your testimony, I believe, states that the legislation places the responsibility of policing physicians and pharmacists on drug sponsors. Would you elaborate on what you mean by that?

Ms. LOEW. That is correct. There is a provision under the distribution and use restrictions that FDA can apply in the REMS which would require sponsors effectively to police how physicians and pharmacists dispense the drug, and we believe that is well beyond the ability and in fact the authority of pharmaceutical companies, and those are authorities that should rest with existing bodies, such as State boards of pharmacies who regulate pharmacists.

Mr. DEAL. Mr. Ubl, would AdvaMed withdraw its support for the user fee legislation of the preemption provision that is in the package? And what would this provision ultimately mean for patients and small device manufacturers?

Mr. UBL. Well, reluctantly, sir, with consultations with our board and our extended membership, it does rise to a level of putting the package in overall jeopardy, in our view. And to get your second

point, particularly for small companies who rely on a more certain environment, particularly those that are funded by venture capital, we view the preemption danger as, again, literally hundreds of State courts, State agencies, State legislators, second guessing the scientists and physicians at FDA. And it was mentioned earlier on the statistic side of things, I think it is important to point out, these cases are going to be decided on an individual basis and the multiplicity of these individual determinations are going to become part of a larger case law that will become what is determined as safe and effective by FDA, and we just think that is a very slippery slope that would raise serious objections.

Mr. DEAL. Mr. Walker, you mentioned in your testimony the phrase manipulating the ideological makeup of the advisory committees. Isn't an ideological conflict of interest just as damaging and even perhaps potentially more damaging to the credibility and impartial nature of an advisory panel, as is a financial conflict of interest?

Mr. WALKER. Absolutely. And if I could expand a bit. In order to understand what is wrong with the advisory committees, you first have to understand precisely how the FDA staffs their advisory committees. The FDA doesn't ask people to join their advisory committees. People can either be nominated or self-nominated. Then those nominations come into the agency and they are given to the office directors in the various offices. That office director goes through that stack of nominees and decides who he wants.

In the case of the advisory committee we watch most closely, which is the oncologic drugs advisory committee, the director literally picks the people he wants and those are the ones that get sent for rubber-stamp approval to the top of the agency. What has happened with the ODAC is that every member of that advisory committee has precisely the same background, precisely the same view of how to conduct clinical trials, and how to make decisions about risks and benefits of drugs, as the office director. And in addition, the office director decides when to call a meeting. The office director decides what questions will be asked. The office director decides what briefing materials they will get. And the office director also decides if he needs consultants who are not current members of the committee, who will sit on the committee. And we have seen, over the last several years, drugs that should have been approved rejected on more or less majority votes based on a single point of view. The Federal Advisory Committee Act requires that these committees be entirely independent of the FDA, in terms of their advice, and they are not.

The other problem we have is that the office directors, and again, with ODAC, can assign members of the committee to work on specific drugs behind the scenes and we think this has happened. In fact, we think we have proof that has happened. And then those people then sit on the committee and vote without disclosure. So we have manipulation of advisory committees and an inappropriate process for putting people on the advisory committees at the FDA.

And in the case of cancer drugs, we call it decelerated approval. There is an initiative underway that was developed by the director of the Office of Oncology Drug Products, on his own, about 4 years ago, to require every single drug, no matter how compelling the

data coming out of phase II, to go into phase III, and it has resulted in 2-year delays in a large variety of drugs, all of which are now approved. But during those delays, people died and it wasn't a small amount of people. It was a lot of people.

Mr. PALLONE. Ms. Schakowsky.

Ms. SCHAKOWSKY. Thank you, Mr. Chairman. I apologize to the witnesses that I didn't hear directly, but I have the testimony.

Dr. Zuckerman, in your written testimony you mentioned recommendations for improving drug safety, including the need to clarify FDA officers' rights to publish scientific articles, as well as the need for strong whistleblower protection provisions. And you said that the right to publish could have meant earlier warnings about the risks of Vioxx and Avandia and others, and I wonder if you could tell us how these additions to FDA law would help us avoid future disasters?

Ms. ZUCKERMAN. Sure. Thank you for asking. I have seen numerous examples where data are presented in public at FDA advisory committee meetings, so it is not a trade secret. It is clear what the data show for a particular product, whether it is Avandia or jaw implants or whatever it is. And when those data show problems, they are basically never published. They are data that a company controls and doesn't choose to publish. They publish the results showing the good news about the products, not the bad news. I don't think that most FDA scientists have a lot of spare time to be writing up articles, publishing these data, but at least if they had that authority to do that and didn't have to worry about losing their jobs. They would have the opportunity to take the data that is already publicly available and publish them in medical journals, and that could have given us a lot of advance notice on Avandia specifically, but other products as well.

Ms. SCHAKOWSKY. Are they currently prohibited from doing that?

Ms. ZUCKERMAN. They are not prohibited so much as they are working in an atmosphere where they are worried about losing their jobs if they do.

Ms. SCHAKOWSKY. Right.

Ms. ZUCKERMAN. So it is more having whistleblower protection that is very clear, that people can't lose their jobs for publishing data that are already public. The other issue is whether they would have to do this in their spare time on weekends and at night, or whether it could be part of their job, which would be great if that were possible.

Ms. SCHAKOWSKY. Mr. Guest, did you want to comment at all on that, the right to publish and the whistleblower protection?

Mr. GUEST. Well, I agree with both of those and that is all part of our notion that there ought to be real transparency about the full information that is available for drugs. Whether it is all clinical trials being public or those who looked at the drug at the FDA and being able to say what they feel about the drug without being in fear of loss of their job, the goal is to get that information out there. We are also supporting, as I said in my testimony, that the action letters that the FDA produces when they approve a drug, that that information also ought to be public and the fact that some people may have dissented in their review. So again, it is all out there so that the public knows, doctors know, and especially

importantly, that other researchers know so they can work with that information at an early stage to either identify or dispel the notion that there may be safety problems. So for all of those reason, we certainly support that notion.

Ms. SCHAKOWSKY. I wanted to ask a bit about the direct-to-consumer advertising. And again, Dr. Zuckerman, I was looking at this document. You talk about that there is going to be—we are going to be seeing, or maybe it is already out and I have missed, campaigns for gastric lap bands, for Botox, for Juvederm, and that there is also going to be an ad campaign for silicone gel breast implants, and that the individuals who give those testimonials are then given free treatment. I don't know. It raises, to me, some ethical questions, but I am wondering—and also, certainly, potential health concerns. I wondered if you would comment on that.

Ms. ZUCKERMAN. Yes, and I got that information from the company's own Web site. There is one company that sells all of those products, Allergan, and it just happens that this one company has decided that direct-to-consumer ads are the way to go, especially for aging baby boomers, and so they are putting a lot of money into really a very attractive ad, an ad campaign. I have seen them on TV. They have a Web site and it says right on there that at least some of the patients who are giving testimonials have gotten free treatment. And as you can imagine, free treatment for some of these things are thousands of dollars, worth a lot of money for what is essentially 2 minutes of taped testimonial.

So there is the concern about—primarily about the fact that these kinds of ads are showing beautiful people very happy and they don't have the risk information provided and maybe they will have, for more information, see our Web site. Or, for more information, see this month's issue of Ladies Home Journal. But they are not providing real risk information. It is not really educating consumers. It is selling a product.

Ms. SCHAKOWSKY. And we baby boomers, who are on a never-ending quest for the fountain of youth, it seems like they may be appealing in a way that could be dangerous to our health.

Ms. ZUCKERMAN. Yes, it really does make it look very quick and easy, whether it is a gastric lap band, which is far from quick and easy, or Juvederm, which is an injection into the face for wrinkles. It is like putting on baby cream or something. I mean, it looks very simple and it doesn't tell you what the risks are.

Ms. SCHAKOWSKY. Thank you. Thank you, Mr. Chairman.

Mr. PALLONE. Thank you. Mr. Burgess.

Mr. BURGESS. Thank you, Mr. Chairman. Dr. Loew, you heard a minute ago a comment made that the Reagan-Udall bill on steroids would be a better way to go with our approach to the FDA. Is that a statement that you would agree with?

Ms. LOEW. I think it is where you fundamentally think about the sort of a system of drug development and approval and managing drugs in the post-marketing setting. There is sort of a big picture hierarchy that is very informative. Essentially, through the development process and into the post-marketing setting, we are doing two things that are distinct and we need to think about a little differently. One is that we are in the process of sort of assessing and managing things that we know about that. Those can be risks.

Those can also be benefits as well, things that we are trying to determine.

The other thing that we are trying to do is to detect unknown risks. So we are in a detection mode as well. And the tools to do those things are quite different, and what FDA has attempted to do through their Critical Path Initiative, which we strongly support, is to develop a new suite of technologies to support both of those things. And so the concept of the Reagan-Udall Institute as a mechanism to further evolve these technologies, and I think particularly relevant to some of the discussions today and also the drug safety hearing that this committee recently held, the concept of developing new tools to monitor risks in the post-marketing setting, through public/private partnership involving many stakeholders, I think is something that is very valuable and that we would very much support.

Mr. BURGESS. Going further into the bill that deals with the risk evaluation and mitigation, what is your opinion about that? Is it overly burdensome? Does it hit the mark?

Ms. LOEW. I think it is a question of focus. Certainly, I think we applaud the committee's efforts to increase the tools available to FDA to manage products in the post-marketing setting and particularly to manage product risks. However, I think there are a couple of things that are important to note. First, focus is important. It would be, I think, unproductive and in fact counterproductive to public health to have FDA's resources thinly spread across all products, when as a matter of practice, they could focus on products and focus more effort and more focused safety activities on products where there are known risks that they wish to continue to manage and assess in the marketplace.

In addition, to go back to the principles that I just set forth to you, we do need to develop new systems to improve the detection of unknown risks. But I think the current construct for the REMS is certainly not an appropriate way to do that and would just lead to unnecessary diversion and dilution of FDA's resources.

Mr. BURGESS. It almost strikes me as if we might be over-legislating and there might be the possibility to take some of the reasonable approaches in the REMS bill and incorporate that into the Reagan-Udall Institute as a single package to try to get the results that we all want.

Ms. LOEW. I think there are a couple of things that I would specifically suggest. There are almost certainly targeted additional authorities that FDA could use productively in the post-marketing setting to help manage drug risks. Those relate to use of post-marketing studies when there is a serious risk that FDA perceives with a product that needs to be assessed. The second is the use of an expedited labeling authority for the FDA to ensure that, in the presence of risk, they are able to go through a process, in discussion with a company, that will bring about rapidly a change to the label that physicians then use to inform their prescribing decisions with patients. And the third is some great focus used in distribution restrictions.

So on the one hand we have, I think, real sort of focused powers that we could give FDA to help. On the other hand, under the concept of the Reagan-Udall Institute that you described, the idea of

evolving new technologies and new tools to try and assess risk in the post-marketing setting is a very valid one and I think one that we would certainly support augmenting.

Mr. BURGESS. Thank you. And I thank all of you for your testimony today. It really has been very interesting to listen to. Mr. Walker, I wanted to ask you a question. You heard referenced earlier the articles in the New York Times yesterday.

Mr. WALKER. Yes.

Mr. BURGESS. And your opinion about the conflict of interest being along the ideological lines, when you read that article, was that something that concerned you, that there was some of this ideological restriction involved?

Mr. WALKER. It concerned me so much that I immediately wrote an e-mail to the author. And there is an ideological problem, but there is also a misperception of what the job of the FDA is and what the jobs of the various people within the structure of the FDA are. The FDA is not a democracy. It is an executive branch agency. They have to make extremely important decisions and they have to be decisions that the public can rely on. We can't have 10 FDAs within the FDA. We can't have anyone who works there deciding they are going to the press and make their own judgment about an FDA decision. I think what happened with Avandia is, again, another great reason why the FDA is far from perfect, but it is our FDA and we have to figure out a way to make it better and we have to figure out a way to make it reliable.

Now to expand on that a little bit more. I own a business. I have been managing scientists for 24 years. Just because someone is a scientist and just because someone feels strongly about their opinion does not mean their opinion is right and it does not mean that it is actionable. And there is a person who was Dr. Lang's boss, whose job it was to make those decisions and it was his or her responsibility to do that. Now, they have made the wrong one, but at that time, that decision may not have been actionable. And what bothered me the most about the article was that there are people that could have given the author that side of the story and it wasn't in the article.

Mr. BURGESS. Well, I would agree with you. I would have never thought I would have come down on the side of defending the FDA, but it is funny how things turn out, isn't it, sir?

Mr. WALKER. And a very strange day for me.

Mr. PALLONE. We have got to move on here, gentlemen. Thank you. Mrs. Capps.

Mrs. CAPPS. Dr. Zuckerman, I have only 5 minutes, but I can't help but offer you a short time, if you wish, to respond to that last statement. But I did want to ask you about advisory committees.

Ms. ZUCKERMAN. OK. Well, I will respond. Thank you. Meta-analysis is a respected, appropriate statistical analysis and what it does it combines a lot of small studies that are too small to have appropriate power for statistical significance and you put them all together and it is a legitimate way. It so happens that my dad was taking Avandia, so I am particular interested in that particular issue because he was swelling up. His whole body was swelling up and now I know why. But the doctor just kept him on it because she thought this was a known side effect and that is OK.

So just to quickly say there are different opinions in science. Yes, FDA has to make a decision, but if a scientist disagrees and then they are punished for it, that is a different issue.

Mrs. CAPPS. Thank you. I wanted to also follow up with you, if I could, on the questioning I gave to Dr. Lutter this morning and maybe it was my way I did it, but I wasn't particularly satisfied with that answer. In your testimony, I was pleased to see that you mention the need for members of the FDA advisory panels who have the need to have members who have no conflicts of interest, and I understand that your organization, the National Research Center for Women and Families, has done some research on advisory committee meetings and patterns in participation among members. So I would like to give you the chance to explain briefly, again, there is not much time, the results of the study that you conducted, why it illustrates the importance of prohibiting scientists with conflict of interest from not only voting but also being part of the discussion because of that persuasive ability? And also, could you touch on the inadequacies of posting vacancies? Again, I wasn't satisfied with the response. The inadequacies of posting vacancies without outreach or some kind of—particular to academia.

Ms. ZUCKERMAN. Yes. Most people in academia do not even know that there are advisory committees at the FDA and that they could participate in them. So if there is no outreach, a whole lot of people will never volunteer, will never self-select. The study that we did looked at about a third of all the advisory committee meetings held between 1998 and 2005, so it was 89 meetings at that time. And we looked at randomly-selected committees and we found that the vast majority of advisory committees were recommending approval, usually unanimously. And when they weren't unanimous decisions, they were usually very lopsided. There were very few where you had a sense that there was a lot of dissention and discussion going on.

So what we found was that one or two people could really control the outcome of any of the votes, because the first people to talk and the people who talked the most were frequently people who had a lot of direct knowledge from financial ties that they had to the company because they had been paid to speak about a product, had received honoraria and so on.

So it was clear that it doesn't matter if the minority of people on a committee have conflicts of interest. Even just one or two people have a lot of sway. And it is a consensus-driven experience. You don't have a lot of argument. It is a very collegial consensus-driven process and very frequently does end up with everyone agreeing to something.

The other thing that I wanted to mention and I do have copies of the report, it is filled with direct quotes that we got from the FDA transcripts, where you have scientists and doctors saying things like I am really not persuaded that this product works, but I am going to recommend approval anyway. Or they will say, gee, I am not sure if this is going to work out, but I hope that it will and I hope that post-market studies will show that it will. And so you have people recommending approval who don't actually think the product is proven safe or effective, and the FDA is sitting there

and not saying a word. They are not saying, "well, but you should judge it on whether you think it is safe or whether you think it is effective."

So for whatever reason, there is a lot of decisionmaking going on at the advisory committee meetings that don't seem in the best interest of patients, because it is not based on whether a product is proven safe or effective, and a lot of people being persuaded by other people on the panel to vote a particular way.

Mrs. CAPPS. Thank you very much. I want to make sure, Mr. Chairman, that we have that report entered into the record, and I just want to get on the record, also, I don't have time, Mr. Guest, and I don't know if we will do another round, but I wanted to express my support for the clinical trial database in the discussion drafts and I wanted you, in writing, if you can, to present a rebuttal to an argument that even the publishing of the presence of a clinical trial is proprietary information. I would like to have more information like that in our records. And can you also write about why it is important for the public health to have a clinical trials database? I am particular interested in how all results, positive and negative, will boost public health. And I think we need to have on the record, even if a drug or a device isn't approved, can't the results of clinical trials perhaps be useful for future innovation and research? And I know there is not time.

Mr. GUEST. I would be happy to supply a prompt and full response to your questions.

Mrs. CAPPS. Thank you very much.

Mr. PALLONE. I just have to ask, Mrs. Capps, that the report that you are asking to be put in the record is which one?

Mrs. CAPPS. The one just now that Dr. Zuckerman mentioned. Maybe it is already in the record.

Mr. PALLONE. Is it something that we have in front of us, Dr. Zuckerman, or not?

Ms. ZUCKERMAN. I didn't include it as part of my testimony, but I am happy to provide it for the record. I have copies here.

Mrs. CAPPS. It is the report of the National Research Center for Women and Families on the advisory, on the study that they did with all of the advisory committees that they reviewed.

Mr. PALLONE. OK. Without objection, we will include that.

Mrs. CAPPS. I would hope so, too. I think that would be an advantage as well.

Mr. PALLONE. Yes, we will get it and we will include it and we will certainly make it available. Thank you. Thank you. Mr. Markey is here.

Mr. MARKEY. Thank you, Mr. Chairman, very much. Dr. Loew, at the time of approval, did the FDA know that Vioxx was going to cause heart attacks and hurt the many patients and families that it did?

Ms. LOEW. I am not able to comment on a product-specific question. I am afraid I have no knowledge to answer that.

Mr. MARKEY. Dr. Loew, at the time of approval, did FDA know that Paxil would actually increase the risk of suicide in kids and result in many parents losing their children to suicide?

Ms. LOEW. I am not able to answer any product-specific questions.

Mr. MARKEY. Dr. Loew, how about fen-phen, did the FDA know about the problems there at the time of approval?

Ms. LOEW. Again, I am not in a position to answer any product-specific questions.

Mr. MARKEY. Dr. Loew, Avandia. Did the FDA know the harm that Avandia was going to do to families in America at the time that the FDA approved it?

Ms. LOEW. I am not in a position to answer any product-specific questions.

Mr. MARKEY. Dr. Loew, I will inform you, then, Dr. Loew, that at the time of approval, neither the companies, I don't think the companies, I hope the companies didn't know, but the FDA did not know about all of the risks of those drugs. Do you agree with that?

Ms. LOEW. I am not in a position to answer that question.

Mr. MARKEY. Yes, I am afraid that is the problem, that PhRMA—I understand why PhRMA doesn't want to have lifecycle monitoring to continue to check in on these drugs to see their impact, and I understand PhRMA's position. It is a legitimate position, but that is not the position which families in America want for these drugs. They want ongoing monitoring of the drugs, after they have been approved, to make sure that new and dangerous information hasn't been developed. So your view is, is that correct, Dr. Loew, if you could, that PhRMA wants to limit the REMS to only those drugs with known serious risks at the time of approval, is that correct?

Ms. LOEW. That is our position and there are currently a number of processes that are in the post-marketing setting to continue to monitor products to try and assess whether there are unknown risks, to detect those risks and then to manage to deal with those. So we actually do support ongoing monitoring, because that exists today and companies do it in a very thorough and rigorous fashion. In addition, we do support and companies do undertake substantial post-marketing commitments. In fact, a recent study by the Tufts Center showed that 73 percent of drug conducting post-marketing studies, those involved in excess of 900 patients. Those are substantial clinical studies. That is in addition to very rigorous post-marketing monitoring, ongoing continuous assessments of adverse event reporting from the passive systems.

In addition, we support, as I discussed earlier, development of new technologies to assess risks. I think that it is widely acknowledged that there are limitations with the current passive adverse event reporting system and we would certainly support, and particularly if we can in a public/private partnership involving all key stakeholders, the evaluation and development of new technologies to assess risk in the post-marketing setting.

Mr. MARKEY. So you object to the language which Mr. Waxman and I have that is recommended by the Institute of Medicine, that would require that the risks are put into a system to regularly review the drugs for the first couple of years that they are on the market?

Ms. LOEW. I think there are a number of things. Firstly, there is already, as I said, in place a system which requires regular assessments of events that are reported.

Mr. MARKEY. No. Why do you object to our language? What is the problem with our language?

Ms. LOEW. Specifically, with regard to the REMS, we believe that the additional authority should be targeted on products where the risks have previously been detected——

Mr. MARKEY. How can you know that, Doctor? You just told me you don't know anything about Vioxx, about Paxil, about fen-phen, about Avandia. You just said you don't know anything, even today, after the fact, you don't know anything.

Ms. LOEW. With the checks.

Mr. MARKEY. So how can you possibly identify the drugs that are going to have the high risks? Don't you need to put in place a system which is going to be able to monitor this risk to families? How can you possibly determine which drugs are going to have these high risks and which aren't?

Ms. LOEW. With respect, I do not have specific knowledge about specific products.

Mr. MARKEY. Precisely why you need a system.

Ms. LOEW. That is because I am not in a position to——

Mr. MARKEY. You are testifying on behalf of the industry. You are here on the last hearing before we begin to mark up.

Ms. LOEW. Thank you. Right.

Mr. MARKEY. If you can't testify on this issue, then no one in your industry knows, because that is what we are debating.

Ms. LOEW. I can't testify about policies. I cannot testify about specific drug examples. What I can testify is that there is actual pre-market testing of drugs provides indication of issues that should be assessed in a post-marketing setting——

Mr. MARKEY. In order to have successful testimony, Doctor, you are——

Ms. LOEW. In order to have legitimacy for supporting a new authority for post-marketing——

Mr. PALLONE. All right, we are over the time here, so I am going to end it, although it was an exciting ending, I must say. Thank you, Mr. Markey. Let me just say in closing, I want to remind all of the members that you can submit additional questions for the record to be answered by the witnesses. I will say to our witnesses, you may get additional questions within the next 10 days and the clerk will notify your offices if that is the case. I do want to thank all of you for being here today. I thought this was a really good, this panel as well as the FDA representative, this was a really good analysis of our drafts and I appreciate the in-depth analysis that you did give them. So thank you very much. And without objection, this meeting of the subcommittee is adjourned.

[Whereupon, at 2:00 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

FDA
ADVISORY COMMITTEES

Does Approval Mean Safety?

A report from
National Research Center for Women & Families

Diana M. Zuckerman, Ph.D.
2006

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EXECUTIVE SUMMARY

FDA Advisory Committees: Does Approval Mean Safety?

The U.S. Food and Drug Administration (FDA) has the responsibility to determine if newly developed medical products are safe and effective. Whether it is a prescription medication, a medication sold over the counter, a medical device, a vaccine, or another type of biologic, the product can be marketed for general sale in the United States only if it has FDA approval.

FDA advisory committees are the most visible part of the FDA approval process. They meet in public to review the most controversial and cutting-edge medical products, examining applications for FDA approval. Committee members discuss the strengths and weaknesses of the studies and their enthusiasm or concerns about the medical product under review. At recent FDA advisory committee meetings on controversial drugs and medical devices such as Vioxx®, silicone implants, and antidepressants, the media have provided the Congress and the general public with a glimpse of the approval process.

Questions have arisen about committee members' financial ties to the companies submitting applications, their commitment to scientific scrutiny, the independence and objectivity of the deliberative process, and inconsistencies between the panel members' expressed concerns and their approval recommendations.

This report describes the results of a study conducted by the National Research Center (NRC) for Women & Families, providing the first objective analysis of the key role of FDA advisory committees as part of the FDA approval process. The purpose of this report is to better understand the strengths and weaknesses of the FDA's advisory committee process for FDA's two largest centers, the Center for Drug Evaluation and Research (CDER) and the Center for Devices and Radiological Health (CDRH).

The study analyzes the voting patterns and committee discussions of a random sample of 6 of 16 drug advisory committees and 5 of 18 medical device advisory panels:

Drug Committees
Antiviral Drugs
Arthritis Drugs
Dermatologic and Ophthalmic Drugs
Gastrointestinal Drugs
Pulmonary and Allergy Drugs
Reproductive Health Drugs

Medical Device Panels
Immunology Devices
Microbiology Devices
Obstetrics and Gynecology Devices
Ophthalmic Devices
Radiological Devices

Data for these advisory committees were collected from the FDA Web site, based on transcripts of advisory committee meetings from January 1998 through December 2005. In that time, the 11 randomly selected advisory committees considered 89 prescription drugs and medical devices, including arthritis medications, LASIK devices, erectile dysfunction drugs, and devices to improve the accuracy of mammograms. There were 866 committee member votes.

Findings

As described by FDA officials, its advisory committees meet only to discuss the most controversial or innovative products, or products whose data are not clear-cut. The public might expect, therefore, that many of the drugs and devices reviewed by advisory committees would not be recommended for approval. The data indicate that this is true for some advisory committees, but not others. Overall, the 11 randomly selected advisory committees recommended approval for 79% of the 89 products reviewed between 1998 and 2005. The device advisory panels were even more likely to vote for approval than the drug advisory committees, recommending approval 82% of the time compared to 76% for drugs.

Despite the controversies surrounding many of these products, the votes for or against approval were rarely close. On the contrary, committee members agreed unanimously for 66% of the drugs and 75% of the medical devices that they recommended for approval.

Drug and Device Approval Recommendations

A review of the meeting transcripts indicates that advisory committee members frequently expressed strong concerns about the safety or the efficacy of the drug or device under review. However, those concerns were not necessarily reflected in their recommendations for approval. There were many examples of committee members who strongly criticized the studies or the medical products under review, and then recommended approval anyway. For example, one committee member indicated after his vote for approval, "Don't take that to mean that I don't have grave concerns about the safety of this drug." FDA officials at the meetings almost never expressed concerns about the disconnect between the committee members' explicitly expressed doubts about safety and effectiveness and their votes in favor of approval.

Of the 50 drug committee voting sessions in the study, 38 (76%) recommended approval of the drug. Most of the votes were unanimous, and almost all (93%) of those unanimous votes recommended approval.

Some of the committees were much more likely to recommend approval than others. The percentage of drugs they recommended for approval ranged from 50% for reproductive health drugs to 100% for arthritis drugs. The percentage of individual votes cast to recommend approval ranged from 50% for reproductive drugs to 98% for arthritis drugs.

What happens after the meetings are over? Of the 38 drugs recommended for approval by the drug advisory committees, all were subsequently approved by the FDA except one drug whose application (at two different dosages) was withdrawn before FDA made its decision. The FDA also approved five (45%) of the 11 drugs that the drug advisory committees voted against, including products that were opposed by almost all the committee members.

Of the 39 device panel voting sessions studied, 32 (82%) recommended approval of the device. Most of the votes were unanimous, with almost all (92%) of those unanimous votes recommending approval.

The percentage of devices that were recommended for approval ranged from 67% for microbiology devices to 88% for ophthalmic devices. The number of panel member votes cast to recommend approval ranged from 57% for microbiology devices to 91% for radiological devices. Three of the five randomly selected devices panels — the Radiological Devices Panel, the Immunology Devices Panel, and the Microbiology Devices Panel — had unanimous support for approval whenever they recommended approval during the eight years of the study.

Almost all (94%) of the devices recommended for approval were subsequently approved by the FDA, and close to half (43%) of the devices that were not recommended for approval obtained FDA approval anyway.

Overall, the study found:

- Many advisory committees recommend approval for almost every product they review, usually unanimously;
- Individual committee members can have a disproportionate influence on approval recommendations;
- Voting patterns differ for drugs and devices, but not when we compare committee members with clinical, scientific, and consumer perspectives;
- Committee members describe pressure to conform and to recommend approval, and they candidly admit that their votes for approval may not be consistent with their concerns about safety and effectiveness;
- FDA officials passively acquiesce when they do not respond to committee members' statements indicating that votes recommending approval are not necessarily based on scientific evidence of safety and effectiveness; and
- The FDA almost always approves products recommended for approval but also often approves products that advisory committees reject.

Implications and Conclusions

The findings suggest that when the FDA schedules meetings for several of its advisory committees, the outcome is almost certainly going to be FDA approval for the products under review. In most cases the advisory committee will recommend approval, but even products that are not recommended for approval are frequently approved by the FDA. Even lopsided votes against approval apparently do not have much weight, since the FDA subsequently approved many of those products.

Although FDA officials describe the advisory committees as providing diverse perspectives and expertise, the large number of unanimous or nearly unanimous votes suggests that either the data are exceptionally convincing or that the committee members are reluctant to disagree with their colleagues or believe that the FDA wants the advisory committee members to come to consensus.

By combining information from the NRC study with studies of conflicts of interest on FDA advisory committees, it is possible to understand how a few committee members with conflicts of interest can have a disproportionate impact on approval recommendations. NRC's analysis of meeting transcripts indicates that many committee members' votes seem inconsistent with their concerns about the safety or efficacy of the drug or medical device under review. These transcripts clearly illustrate the pressures that committee members describe to conform to their colleagues or to be able to vote "yes" even if it means changing the wording of the question so that they can do so in good conscience. The report includes examples of committee members directly trying to influence the views or votes of other committee members.

If the FDA is relying on advisory committees to help determine the conditions of approval, one would expect that FDA officials would provide explicit oral instructions about the types of conditions that the FDA is willing to impose, and that the FDA would impose most of the conditions and then enforce them. That is not the case, however.

Committee members frequently recommended unenforceable or vaguely worded conditions of approval and expressed their intention to recommend approval for products that they did not believe were proven safe or effective. Their candor suggests that they would welcome guidance from the FDA officials present, to make sure their recommendations were appropriate. Nevertheless, during committee discussions FDA officials showed remarkably little interest in providing oral guidance regarding the criteria for approval, or the realities of approval conditions to advisory committee members during the eight years analyzed in the study. Conditions of approval imposed by the FDA often did not reflect the conditions recommended by the advisory committees. Conditions that were imposed were rarely enforced.

Overall, the findings indicate that committee members, intentionally or unintentionally, move toward a consensus that often seems inconsistent with their differing views or perspectives in making decisions that may have life-or-death consequences for millions of Americans. Voting for approval contingent upon conditions is a popular compromise, but the FDA does not impose most of the specified conditions on the companies when it grants approval. The committees' tendency toward approval seems to reflect the FDA's goals; in fact, the FDA appears to be even more geared toward approval than the advisory committees. The FDA approved almost all the prescription drugs and devices recommended by the advisory committee, and also approved almost half the products that were opposed by the committee members.

Whatever the reasons, many of today's FDA drug and device advisory committees are rubber stamps for approval almost every time they meet. Moreover, even when an overwhelming majority recommend "non-approval," there is a good chance that FDA officials will approve the product anyway. Approval is even more likely for medical devices than it is for drugs.

Recommendations

If the goal is to restore confidence in the FDA, and restore the independence that FDA advisory committees were intended to provide, it is essential that the FDA make changes in the policies and process governing its advisory committees. The following recommendations are based on the assumption that the Congress and the FDA are committed to that end:

1. **The FDA should stop granting conflict-of-interest waivers for committee members, except under very restricted conditions.**
2. **The FDA should provide explicit and specific oral guidance whenever needed during advisory committee meetings regarding appropriate criteria for safety and effectiveness, and appropriate criteria for conditions of approval.**
3. **The FDA should demand more from advisory committee members, and then be more responsive to their concerns.**

INTRODUCTION

FDA Advisory Committees: Does Approval Mean Safety?

The U.S. Food and Drug Administration (FDA) has the responsibility to determine if newly developed medical products are safe and effective. Whether it is a prescription medication, a medication sold over the counter, a medical device, a vaccine, or another type of biologic, the product can be marketed for general sale in the United States only if it has FDA approval. This report is based on the first study to objectively examine the key role of FDA advisory committees as part of the FDA approval process. The purpose of this report is to examine the decision-making process and voting patterns of FDA advisory committees considering approval for new medical products or new medical indications for previously approved products at FDA's two largest centers, the Center for Drug Evaluation and Research (CDER) and the Center for Devices and Radiological Health (CDRH).[i]

■

FDA advisory committees meet to review the most controversial and cutting-edge medical products. When these products are approved and later found to be more dangerous than expected, it is important to determine what went wrong.

■

FDA advisory committees are the most visible part of the FDA approval process. They meet in public to examine applications for FDA approval, discussing the strengths and weaknesses of the studies and committee members' enthusiasm or concerns about the medical products. At recent advisory committee meetings on controversial drugs and medical devices such as Vioxx®, silicone implants, and antidepressants, media coverage has provided Congress and the general public with a glimpse of the approval process, and the advisory committee decision-making process has come under criticism. Questions have been raised regarding committee members' financial ties to the companies with applications before the advisory committee, their commitment to scientific scrutiny, the role of patients' subjective testimony, and apparent inconsistencies between the committee members' expressed concerns and approval recommendations.

FDA advisory committees meet to review the most controversial and cutting-edge medical products. When these products are approved and later found to be more dangerous than expected, it is important to determine what went wrong, and whether it is possible to strengthen the safeguards without delaying the availability of life-saving products. In order to understand the FDA approval process for specific medical products, however, it is essential to examine how advisory committees work in general.

By analyzing the committee members' voting records and public discussion of approval decisions, this report sheds light on how the advisory committee process trends toward consensus and approval, and how individual committee members can have a disproportionate influence on approval recommendations. The report examines how highly controversial products can generate little disagreement among accomplished professionals representing a wide range of perspectives and expertise. In addition, this report determines the extent to which voting patterns differ for drugs and devices, and for committee members with clinical, scientific, and consumer perspectives. Based on our findings, NRC for Women & Families recommends changes that will strengthen the scientific basis and influence of FDA advisory committee decision-making.

FDA Advisory Committees: The Basics

The company whose product is under consideration for FDA approval is responsible for providing data to the FDA that proves its product is safe and effective. For most medical products, the FDA makes an approval decision based on its internal reviews of available data, almost all of which is provided by the company. Agency scientists review the research data and other information, and FDA officials make the final decisions.

[i] The FDA refers to each advisory committee at the Center for Drug Evaluation and Research as a committee, and refers to the individual device advisory groups at the Center for Devices and Radiological Health as panels. For the purposes of this report, we make that distinction when possible but sometimes use those terms interchangeably.

Sometimes the FDA seeks additional advice, particularly on emerging technologies or controversial medical products. If the approval decision is unclear or controversial, or if there is substantial disagreement within the FDA, the FDA usually consults a scientific advisory committee whose members are selected and paid by the FDA but are not FDA employees. The FDA has 16 scientific advisory committees to review drugs and 18 to evaluate medical devices. The committees divide along product lines and body systems (such as arthritis drugs, reproductive drugs, reproductive devices, and ophthalmic devices) and review the products at public meetings that usually last one or two days. Members have overlapping terms for up to four years, and the terms are rarely renewed. The advisory committee meetings, open to journalists and the public, take place at hotels in the greater metropolitan Washington, D.C. area. Committee members receive data and analyses provided by the company whose product is under review, as well as a review memorandum and additional information provided by FDA scientists.[ii] Much of that information is publicly available online at least one day before the committee meeting.

Advisory Committee Meeting Agendas. During the public meeting, the company sponsor presents its data; the FDA scientists present their review; members of the public are invited to speak briefly during the "open public comment period"; and committee members ask questions of the sponsor, the FDA, and occasionally individuals who speak during the open public comment period. At most advisory committee meetings, most of the research-based presentations are by the company and its paid consultants, with less time for presentations by FDA scientists. Outside experts, such as government researchers or independently funded researchers, are sometimes invited to make formal presentations at an advisory committee meeting, but such presentations are not typical. In an announcement published in the *Federal Register*, members of the public are invited to sign up in advance if they want to speak. They must come at their own expense and usually are only given a few minutes to speak. Many meetings have no speakers during the open public comment period. At the most controversial committee meetings, where more than 100 individuals may ask to speak, each is likely to be given only two or three minutes. These time limitations are a disincentive to testify, since the cost of traveling to the meeting can be prohibitive; the hotel rooms where the meetings take place often cost more than $150 per night, and the hotels are frequently not near an airport or public transportation. In contrast, the company whose product is under review and others who support approval often pay transportation costs for patients, physicians, and others willing to testify on behalf of the product during the open public comment period. When they do so, part of the public comment period may be an extension of the company's strategy to get FDA approval.

After listening to the company presentation, the FDA presentation, and any public comments, committee members discuss and vote on questions that the FDA has prepared and provided to committee members in advance. The prepared questions for new medical products include whether the product is effective, whether it is safe, and "whether the safety and effectiveness information submitted for a new drug is adequate for marketing approval." [1] The safety and effectiveness questions for medical device advisory panels are somewhat different. For devices, safety is defined as a reasonable assurance based on valid scientific evidence that the probable benefits to health outweigh any probable risks. Effectiveness is defined as a reasonable assurance that a significant portion of the population will have clinically significant results.[iii] Additional questions often concern labeling information that committee members would recommend if the product were approved. In other words, although part of the meeting is to determine whether the committee will recommend approval, the committee members are told before the meeting that they will be asked to consider the conditions of approval, including what warnings or indications to put on the label. Depending on the wording, this has sometimes aroused criticism for giving committee members the impression that approval is expected, possibly creating a climate that pressures them to approve a product with conditions or restrictions, rather than rejecting it based on safety concerns.

[ii] For the purposes of this report, all individuals serving on a committee are referred to as committee members, although some are members of the standing committee and others were added to the committee for only one or more meetings. Meetings average 10 voting members.
[iii] These definitions are included in the charge to the medical device panels, and are read to the panel as part of a boilerplate set of instructions before voting begins.

Committee Members. Most committee members are physicians or scientists with expertise in the general area but not necessarily regarding the specific type of product under review. Advisory committees also include one industry representative and one patient or consumer representative. On medical device advisory panels, these representatives may ask questions and make comments but not vote. In the drug advisory committees, the patient or consumer representative is a voting member, but the industry representative may not vote. In addition to the permanent members of the advisory committees, the FDA frequently will add one or more temporary members to each committee meeting with expertise relevant to the specific product under review.

According to Linda Ann Sherman, the FDA's director of advisory committee management and staff, the FDA's advisory committees' role is "to offer the FDA the very best advice possible on related questions posed by the Agency on a product of regulated industry."[2] She explains that "Scientific advisory committees complement the Agency's scientific expertise by bringing cutting-edge research, patient and patient caregiver concerns, and industry and consumer advocacy viewpoints to the table for discussion." In addition, the advisory committees "lend credibility to the FDA decision-making processes by having public discussions of controversial topics by the world's experts, the Agency staff, and the Agency's stakeholders (industry and consumers)." FDA advisory committees are balanced demographically and scientifically, and are intended to be representative of the country in terms of age, race, sex, ethnicity, and other factors.

The decision to involve an advisory committee is usually at the discretion of the division director in one of the FDA's five product centers. Linda Kahan, deputy director of FDA's Center for Devices and Radiological Health, explains that the purpose of the advisory committee process is "to air issues that are controversial, complex, and do not have simple answers."[3]

The advisory committee process is expensive and time-consuming for the companies and the FDA, as well as for members of the public who take the time to travel to the meeting and participate. The FDA pays committee members' travel expenses as well as honoraria, but that reimbursement is unlikely to pay for all their time if they carefully review the data and documents before the meeting. The FDA Inspector General reports that about 21% of drug approvals were preceded by an advisory committee meeting.[4] The percentage is much lower for medical devices, since most medical devices are cleared for market without going through the Pre-market Approval (PMA) process, and therefore are exempt from scrutiny by FDA advisory committees.[5] Even so, in fiscal year 2003, FDA's advisory committee process "conservatively cost taxpayers more than $8 million."[2]

Although the FDA generally follows the advice of advisory committees, the agency is not required to do so.

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Advisory committees have increasingly been criticized by Congress, the media, and consumer advocates because of questions about the committees' objectivity and scientific scrutiny.

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Controversy and Questions

One hundred years ago, the FDA was created in response to concerns about dangerous and ineffective medical products. In recent years, the FDA has come under scrutiny when numerous widely used FDA-approved drugs and medical devices were recalled or removed from the market in the wake of reported deaths and serious illness. In some cases, such as the painkiller Vioxx®, the products were approved by the FDA after unanimous recommendations from FDA advisory committees. The advisory committees have increasingly been criticized by Congress, the media, and consumer advocates because of questions about the committees' objectivity and scientific scrutiny. The focus, however, has been on drug approvals, not on medical devices. For example, an investigative journalist at *USA Today* found that at 92% of the drug advisory committee meetings from 1998-2000, at least one committee member had a financial conflict of interest.[6] Similarly, a more recent study published in the *Journal of the American Medical Association* found that at 73% of FDA drug advisory committee meetings from 2001 through 2004, the FDA announced that at least one voting member had a financial conflict of interest; at 22% of the meetings, more than half the advisory committee members had such conflicts.[4] The researchers pointed out that conflicts of interest could have influenced voting patterns because they "typically produced overall votes more favorable" toward the drug.

STUDY DESIGN

This report describes the findings of a study conducted by the National Research Center for Women & Families, which analyzed the voting patterns of a random sample of FDA advisory committees. The goal of the study, the first of its kind, is to evaluate the pattern of approval recommendations made by FDA advisory committees at two FDA centers, the Center for Drug Evaluation and Research and the Center for Devices and Radiological Health. A random sample of 6 of 16 drug advisory committees and 5 of 18 medical device advisory panels was analyzed in terms of voting patterns from January 1998 through December 2005.

Advisory committees typically are asked to answer specific questions about medical products under review by the FDA. Generally, FDA questions include whether the data indicate that the product is safe and effective, and whether the data on safety and effectiveness are adequate to support approval for marketing. Committee advice is not limited to questions related to new-product approval and marketing, however; committees also review new information about disease indicators and applications for new indications in FDA-approved medical products. Committee members may vote that the FDA require additional studies or make changes to a product's labeling. Sometimes advisory committees even make recommendations outside of the scope of the FDA's questions.

This study analyzed only those votes dealing with the FDA approval of a New Drug Application (NDA) or new indication for a previously approved drug, or a PMA for devices. On those rare occasions when a committee member abstained, that vote was not included in the analysis.

The advisory committees included in this study are as follows:

DRUG COMMITTEES
Antiviral Drugs
Arthritis Drugs
Dermatologic and Ophthalmic Drugs
Gastrointestinal Drugs
Pulmonary and Allergy Drugs
Reproductive Health Drugs

MEDICAL DEVICE PANELS
Immunology Devices
Microbiology Devices
Obstetrics and Gynecology Devices
Ophthalmic Devices
Radiological Devices

Data for these advisory committees were collected from the FDA Web site, based on transcripts of advisory committee meetings from January 1998 through December 2005. In that time, the six drug and five device advisory committees that were randomly selected considered 89 medical products at public meetings. There were 866 committee member votes.

Information about the products reviewed by these committees is included in Appendix C and Appendix D.

Advisory Committee Voting Patterns

As described by FDA officials, its advisory committees meet only to discuss the most controversial or innovative products, or products whose data are not clear-cut. Based on the FDA's concerns about the lack of "simple answers" for these products, the public might therefore expect that many of the drugs and devices reviewed by advisory committees would not be recommended for approval. The data indicate, however, that the 11 randomly selected advisory committees recommended approval for 79% of the 89 products reviewed between 1998 and 2005. The device advisory panels were even more likely to vote for approval than the drug advisory committees, recommending approval 82% of the time compared to 76% for drugs.

Despite the controversies surrounding these products, the votes for or against approval were rarely close. On the contrary, 75% of the medical device approval recommendations were unanimous, as were 66% of the recommendations for drugs. The votes against approval were less likely to be unanimous: 29% of devices and 15% of drugs that the committees rejected were unanimous votes.[iv]

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Scientists are taught to scrutinize and criticize data from the perspectives of their academic disciplines. Similarly, the popularity of "second opinions" in medicine reflects the diversity of physicians' views on medical treatment and safety matters. Although FDA officials describe the advisory committees as providing diverse perspectives and expertise, the large number of votes that are unanimous or nearly unanimous suggests that either the data are exceptionally convincing — providing overwhelming evidence that the product is safe and effective — or the committee members are reluctant to disagree with their colleagues or believe that the FDA wants the advisory committee members to come to consensus.

For drugs and devices, most recommendations for approval were accompanied by warnings and restrictions on the label or specific conditions regarding additional research. In most device approvals there were numerous conditions, ranging as high as 14 for one device. Perhaps, therefore, the primary function of the advisory committees is to recommend restrictions and warnings on the labels and the conditions of approval, rather than to determine whether a product should be approved. This could explain the FDA's description of the use of advisory committees to examine complicated products and issues. However, if the FDA is relying on advisory committees to help determine the conditions of approval, including post-market research, one would expect that FDA officials would provide clear instructions to the advisory committees about the types of conditions that the FDA can mandate, and that the FDA would then enforce them.

One also would expect that the conditions of approval recommended by the advisory committees would be similar to those that the FDA required of the manufacturers. The findings do not support this.

In an effort to understand the advisory committee process, we examined the voting patterns of specific committees as well as individual members and types of members. The results indicate that certain advisory committees have recommended approval for every product they have reviewed for many years. There were individual committee members who never voted against approval of any product they reviewed. There also were

[iv] These differences were not statistically significant, reflecting the relatively modest sample size and the high proportion of recommendations for approval and unanimous recommendations in both device and drug advisory committees. The analyses were conducted using 2 x 2 *chi square* comparisons.

advisory committee members who never voted in the minority; in other words, if the majority voted against approval, they also voted that way, and if the majority voted for approval, they always voted that way.

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The results indicate that certain advisory committees have recommended approval for every product they have reviewed for many years.

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The Ophthalmic Devices Advisory Panel is an example of a panel that does not seem to be especially discriminating, having recommended approval for every medical device they considered for the last six years. The 10 medical devices they supported included implantable contact lenses, a capsular tension ring to aid in cataract surgery, and LASIK devices. Do the 100% approval recommendations mean that the ophthalmic devices reviewed by the FDA during those years were especially safe and effective, so that even the most controversial and complicated devices had data that clearly supported safety and effectiveness? On the contrary, in 2006, ophthalmic devices made the headlines when one of the major ophthalmic device manufacturers, Bausch & Lomb, withdrew one its newest contact lens solutions, ReNu® with MoistureLoc, from the market after reports of eye infections and blindness associated with its use. Did the FDA advisory panel fail to properly scrutinize this product?

Our analysis finds that the Ophthalmic Device Advisory Panel never reviewed ReNu® with MoistureLoc, because it was not considered a controversial product that needed careful scrutiny. On the contrary, ReNu® with MoistureLoc was cleared for market by the FDA as a medical device in 2003 under the 510 (k) program, which allows devices to be approved without clinical trials or advisory panel scrutiny if FDA agrees with the manufacturer that the product is substantially equivalent to other medical devices that are already on the market. The 510 (k) process provides much less scrutiny than the PMA process, and only the most controversial devices in the PMA process are reviewed by FDA advisory panels. Therefore, the medical devices reviewed by this advisory panel are considered much more controversial or innovative than ReNu® with MoistureLoc, which was subsequently removed from the market because of serious risks. Although the explanation of why ReNu® users developed rare eye infections has not been publicly revealed, FDA inspectors noted that the formula for the contact lens solution had been changed but that no clinical trials were conducted to determine if it was safe or effective if used as directed.[7] This example shows that ophthalmic devices have serious risks as well as important benefits, and certainly the most innovative and complicated ones, which are reviewed by the advisory panel, deserve careful scrutiny.

Diversity of Opinion: Who Votes For Approval?

As can be seen from the high proportion of recommended approvals, most advisory committee members recommend approval most of the time. Nevertheless, it is possible that committee members' training or perspectives may account for differences in voting patterns, with scientists potentially more skeptical about the data and practicing physicians more enthusiastic about new medical products because they can provide greater treatment choices. Consumer representatives might be especially concerned about risks or especially interested in getting new products approved and available. To evaluate differences in voting patterns, we categorized committee members in one of four groups: physician only (M.D. or D.D.S.); physician plus scientific degree (M.D. plus Ph.D. or master's degree); doctorate only (Ph.D., Sc.D., or Pharm.D.) and consumer representative (several of whom had R.N., M.P.H., or doctoral degrees). We analyzed the voting patterns of these four groups separately for the drug advisory committees and the device advisory panels. The few committee members with degrees that did not fall in these categories, such as law degrees, were not included in the analyses.

Drug Advisory Committees. The drug advisory committees included 155 committee members with medical degrees only; 46 with medical degrees plus a scientific degree; 62 with scientific degrees only; and 17 consumer representatives. We separately analyzed the data for the three patient representatives.

Of the 288 votes of the physician members, 210 (73%) were for approval. Of the 92 votes of doctoral level members, 67 (73%) were for approval. Of the 89 votes of the physician scientists, 71 (80%) were for approval. Of the 36 votes of consumers, 27 (75%) were for approval. There also were three patients who voted on these committees, and 100% were for approval. Clearly, our expected differences in voting patterns did not emerge; on the contrary, the doctors, scientists, and consumers voted identically, and the physician scientists were slightly, but not significantly, more likely to vote for approval. Although the 100% approval votes of the patients on the committees is interesting, the sample is much too small to draw any conclusions other than that patients tended to vote for approval as the other groups did.

Medical Device Advisory Panels. Consumer and patient representatives are not permitted to vote on device advisory panels, so we compared the 78 physicians, 14 physician scientists, and 31 scientists. Of the 207 votes of the physician members, 161 (78%) were for approval. Of the 72 votes of doctoral level members, 60 (83%) were for approval. Of the 32 votes of the physician scientists, 26 (81%) were for approval. As with the drug advisory committees, there is virtually no difference among the three groups.

Drug Advisory Committee Members Explain Their Votes

The FDA provides a full transcript of each committee meeting on its Web site, enabling our researchers to carefully review the questions and discussion, the concerns and enthusiasm expressed, and the reasons each committee member gave when voting. We assumed that overall, committee members expressing enthusiasm for a product would vote for approval and those expressing strong concerns would vote against approval. Therefore, we focused on the exceptions to that general pattern. We examined whether the surprisingly high proportion of votes in favor of approval could be explained by motivations other than confidence in the safety and effectiveness of the medical product under consideration. In this section of the report, we will focus first on comments from members of the Arthritis Drugs Advisory Committee, which had the highest proportion of votes for approval of all drug or devices advisory committees.

Arthritis Drugs Comments. The 33 members of the Arthritis Drugs Advisory Committee during 1998-2005 reviewed seven new drugs during the eight years of this study, two of which they voted on for two different indications in two different years. Of the 83 recorded votes they cast for these seven drugs, 81 (98%) were for approval. Only two committee members ever voted against approval, and each did so only once.[v]

Given that advisory committees are convened for the most controversial or cutting-edge products, this near unanimity in voting is striking and worrisome. The findings are especially important because they included unanimous approval for Celebrex® in 1998 and Vioxx® in 1999, two drugs that subsequently were found to be associated with increased risk of heart attack and stroke. Vioxx® was subsequently removed from the market; Celebrex® remains on the market, but with strong warnings.

There are several possible reasons why drugs would unanimously be recommended for approval and then later be found to be more dangerous than expected:

1. Committee members might have relatively lenient standards for approval, lack understanding of statistical or scientific shortcomings of the data, or both;

2. The research findings provided to committee members might be reassuring and convincingly presented and the risks may not be fully determined until the product is used long term or on patients that differ in age, health status, or other traits that influence safety; or

3. Committee members might feel pressure to recommend approval for the product or pressure to conform with colleagues on the committee who support approval.

[v] When the advisoey committee met to review a new indication for the previously approved Enbrel® in 2000, the vote was stated as 7-2 for approval in the meeting transcript. However this vote was not included in the study statistics because it was not a roll call vote and committee member votes were not recorded in the transcript.

As we consider whether the committee members are relatively lenient in their standards for approval, the question arises as to whether they carefully scrutinize the statistical analyses that are the basis of proving safety and effectiveness. Since most of the votes are cast by physicians, and physicians who do not have research degrees do not necessarily have statistical training, it is possible that the lack of statistical expertise could make it difficult for some committee members to scrutinize the inferential statistics presented.

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"Since I'm ignorant of most statistical issues, in my ignorance I can be very impressed with the data."

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The FDA meeting transcripts do not indicate how often this happens, but several committee members clearly stated their lack of understanding of the data. For example, at the August 1998 Arthritis Advisory Committee meeting on Arava®, Dr. Steven Abramson stated: "Since I'm ignorant of most statistical issues, in my ignorance I can be very impressed with the data." [8] Although other committee members also had difficulty understanding the data analyses, most were not as candid.

Within a few years of this advisory committee meeting, Arava® was associated with 130 severe liver reactions, including 56 hospitalizations and 22 deaths. As a result of these publicized adverse reactions, the Arthritis Advisory Committee met in March 2003 to determine if "the benefit to risk profile" of Arava® was acceptable for the current indications. At that time, Dr. James Fries expressed his view that risk information should not be considered unless the data are conclusive. He explained, "I have this sort of gorge that rises when we have groups which are watchdogs for the public interest who may be hurting the health of the public by raising what turn out to be false positive red flags. Now, I'm in favor of eternal vigilance, but until we actually have something that rises up out of background I don't think we ought to mention it." [9] Once again, the committee voted unanimously to maintain approval. Arava® is still on the market, but the FDA now warns patients that the drug can cause "rare cases of severe liver injury, including death" as well as inflammation of lung tissue. Patients taking Arava® must have their livers tested before use, and regularly while they are taking the drug.[10]

In August 2001, the Arthritis Advisory Committee met to review Kineret® for treatment of rheumatoid arthritis. During that meeting, several committee members indicated that they understood that FDA's standards for approval do not require proof of safety and efficacy. For example, Dr. Jennifer Anderson remarked that she questioned whether the data "demonstrate an appropriate safety and efficacy profile as a treatment. I don't think that has been shown yet, but that is not what we are voting on." [11] Despite those doubts, she concluded that "the data are adequate, it seems, for approval given the way the guidelines for these things are written by the FDA." The patient representative, Leona Malone, expressed her uncertainty and ambivalence, stating "I am anxious for anything to come out that is going to offer some help" to patients but "I am not familiar with clinical data enough to really cast a vote in the same type of league with you people, but it does fulfill the requirements that FDA set up. So, I would say a very quiet yes." In a response that was unique for the advisory committee meetings in the study, Dr. Jay Siegel, an FDA employee participating in the meeting, disagreed with the committee members' comments and clarified FDA requirements for approval, saying, "Wait a second. The law requires that a drug be safe and effective for approval, and there seems to be a lot of confusion about these guidelines and what they mean, because there have been three comments that this meets the standards for approval, but we are not sure about whether it is actually good."

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Dr. Siegel's comments were highly unusual, and at other meetings, FDA officials did not respond when advisory committee members clearly expressed their intention to vote for approval of products that they were not sure were safe or effective. The standards for products already on the market may be especially lenient and the

pressure to agree with committee members who vote for approval even greater, based on the numerous concerns expressed about a new indication for Enbrel® at the April 2000 advisory committee meeting. During the discussion before voting, Dr. David Felson did not comment, but after Dr. Steven Abramson expressed concerns about the lack of long-term safety data and said "I would still wait another year" before approval, Dr. Felson agreed, admitting "I didn't have the courage to say what you said. I've sort of been leaning on the fence in terms of thinking about this problem because I think there's wonderful efficacy data here, and the safety data is genuinely reassuring, I think, despite all the concerns we all had. But the truth is I wouldn't want to give a patient with early rheumatoid arthritis this treatment without some better data on long-term safety. I wouldn't want to sentence them to potentially having a really dangerous long-term side effect without knowing more, especially since there's nothing keeping them from ultimately getting it [since it is already approved]...I think that remains my concern. I'm still not sure, though. I think I could be convinced either way." [12]

At the same meeting, Dr. Nigel Harris stated that since Enbrel® was already approved and already in use, "Indeed, if there is a risk that we don't know, the risk will exist and occur anyway....You know, let us approve it as a first line — not first line but as a first stage. If there's trouble down the road, you're going to get it anyway. We've approved it, and the trouble will occur. So really, I think that, one way or another, the concerns about safety really are not important in terms of what we are considering today." [12]

When Dr. Lee Simon expressed his desire "to see if I can sway you one more time," Dr. Abramson interrupted, saying, "I was already swayed. I didn't want to be like a wimp and be inconsistent." The comments for Enbrel® suggest that new indications may be held to an even less stringent standard than new products, since it is widely assumed that they can be used off label for other indications anyway.

These are just a few of the comments that indicate that Arthritis Drugs Advisory Committee members sometimes voted for approval despite strong concerns. It is notable that FDA officials usually made no effort to encourage stricter approval standards. Nor is this pattern unique to the Arthritis Drugs Advisory Committee. The comments of members of other advisory committees with less extreme voting patterns expressed similar concerns and the FDA was similarly acquiescent. A few of the many examples are quoted for each committee.

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"If we don't expect certain standards, then the message gets out that someone else can come in and not do a good job or not present these things, and that also bothers me."

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Antiviral Drugs Committee Comments. Several members of the Antiviral Drugs Advisory Committee also indicated that they were bowing to pressure to conform. At the January 1998 meeting on CellCept®, the committee voted unanimously to recommend approval, despite very strong concerns. For example, the consumer representative, Susan Cohen, stated: "Since I'm not a political person, I really have tremendous problems with the samples they used....It really troubles me a great deal. I think they were chosen to be favorable, and so I'm not comfortable with that. The other thing I have to say that makes me uncomfortable — being [a] consumer member is a lot different. If we don't expect certain standards, then the message gets out that someone else can come in and not do a good job or not present these things, and that also bothers me; because I'm here representing consumers, and that's what it's about, and thank God someone mentioned at this table consumers....I think I'm going to have to vote yes, but with a lot of reservations and concerns that this doesn't send a message out to every other pharmaceutical company, well, you know, in the long run you can get it passed, but I am troubled about how you put your samples."[13]

Doctors on the committee also described the pressure to conform and please colleagues. At the July 1999 meeting of the Antiviral Drugs Advisory Committee to

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"I'm going to have to vote yes, but with a lot of reservations and concerns that this doesn't send a message out to every other pharmaceutical company, well, you know, in the long run you can get it passed."

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review Rapamune®, Dr. Lawrence Hunsicker stated, "So one of the things that has to be put on as a caveat is that we do not know the safety of this drug beyond one year. Now, when mycophenolate was presented I almost lost all my friends by proposing that we actually put a one-year limit on the labeling. And I was talked out of it by my friends who told me that if they didn't talk me out of it they'd outvote me anyway. So I'm not going to make that recommendation."[14]

The advisory committee members' desire to approve drugs is sometimes so strong that they change the criteria for approval, ignoring whether a product is efficacious. For example, at the February 2001 Antiviral Drugs Advisory Committee meeting reviewing Valcyte®, a drug to treat eye disease related to HIV infection, committee members were asked if the data supported the efficacy of the drug for maintenance therapy. Several committee members stated that the data did not support efficacy of the drug, so Dr. Ram Yogev asked if the word "efficacy" could be replaced with the word "use" so that they could instead vote on whether the data supported the "use" of the drug. Rather than clarify the criteria for approval, as Dr. Siegel did at the Arthritis Committee meeting that same year, Dr. Debra Birnkrant, the Acting Director of FDA's Division of Antiviral Products, agreed to the change. The committee chairman then asked if replacing "efficacy" with "use" would make committee members happy, and Dr. Yogev replied, "Much happier, because then I could say yes....I don't know the efficacy."[15] The committee subsequently recommended the drug for approval by a vote of 11-1.

Dermatologic and Ophthalmic Drugs Comments. Similar pressures were expressed at the March 2003 review of Vitrase®, a drug to treat bleeding in the eye, by the Dermatologic and Ophthalmic Drugs Advisory Committee. When the committee was asked if they thought there was evidence that the drug was effective, eight committee members voted no and only four voted yes. Nevertheless, when asked if the benefits outweighed the risks, they voted 7 to 5 for approval. In other words, three committee members voted that the benefits outweighed the risks even though they had voted that the drug had no proven benefits. Dr. Scott Steidl admitted the contradiction, explaining, "I am a little confused about this question, personally. But...my feeling is similar to what Stephen Feman stated that, although I said no to the first [question regarding effectiveness], I am thinking about the last question in a broader sense. So I guess you could put me as a yes. I think there probably are subsets and patients where I would consider it so I kind of feel that I would have to say yes to this even though it may seem contradictory."[16] The votes would seem less contradictory if the product had no substantial risks, but that was not the case; the FDA required the Vitrase® label to list numerous risks, and later criticized the company for failing to provide adequate warnings about these risks in their advertising.[17]

Gastrointestinal Drugs Comments. Sometimes the pressure to save time also may undermine the process and result in consensus rather than argument. That consensus can be for or against approval. For example, at the June 2000 meeting of the Gastrointestinal Drugs Advisory Committee, the chairman, Dr. Stephen Hanauer, interrupted himself as he was about to read the warnings regarding Zelmac®, a drug for irritable bowel syndrome, saying, "Gee, I really don't want to read this whole thing. It is on the bottom of page 6...." and Dr. Christina Surawicz interrupted, reassuring him: "We have read it. It is good."[18] The committee then voted 1 to 7 against approval. Two years later, the FDA approved the drug with a new name, Zelnorm®, and published a Talk Paper on the FDA Web site that incorrectly referred to the product as recommended for approval by the Gastrointestinal Advisory Committee in June 2000.

At a March 2003 meeting of the same advisory committee to review Emend®, votes for approval did not always reflect confidence in the product. For example, Dr. Robert Levine admitted, "I'm uncomfortable with it, but I will say yes. From these other experiences with post-marketing, as all of you are saying, these are very serious consequences. Therefore....I would say yes."[19]

Pulmonary and Allergy Drugs Comments. At times, advisory committee members are explicit in their uncertainty of how to vote. In September 2003, the Pulmonary and Allergy Drugs Advisory Committee reviewed Ariflo®, a drug to improve pulmonary function. Dr. Carroll Cross could not decide how to vote and stated, "My answer is maybe but I have to decide which way to go. Can I pass for now and listen to other comments as we go around the table?"[20] Although it is certainly desirable for committee members to learn from the views of colleagues with different perspectives, generally that sharing of ideas should take place during the many hours of presentations, questions, and discussion. His request to delay his vote illustrates how the votes of committee members with strong opinions can directly influence the votes of their colleagues.

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"It's kind of like old-fashioned medicine: It's not much good, but it probably won't do much harm either."

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Reproductive Drugs Comments. The Reproductive Drugs Committee was least likely to vote for approval, but, even so, committee members sometimes voted for approval after expressing very strong concerns. For example, at the April 2000 review of Uprima® by the Reproductive Drugs Advisory Committee, Dr. Robert Califf described the low standards for approving the erectile-dysfunction drug, saying, "Specifically with regard to the 2-milligram dose, it seems to me that as a specific question, it's kind of like old-fashioned medicine: It's not much good, but it probably won't do much harm either." He later indicated that any advantage of the product might be more psychological than physiological, suggesting, "Maybe it would be best to start with placebo."[21]

The committee members' comments regarding Uprima® clearly show that a vote for approval does not necessarily mean that advisory committee members believe that a product should be approved. For example, Dr. Peter Kowey admitted, "If you came back and told me several months from now that you decided not to approve this drug, it would not break my heart because I think there are two ways to handle this kind of problem. One way is to not approve the drug. Period. And the other way is to approve it and then label the hell out of it. I voted yes with the proviso that you understand that there's got to be a tremendous amount of work done on labeling for this drug. I favor a black box warning in bold letters that says, that if you take this drug, you may pass out and if you pass out, you may injure yourself and you may injure yourself severely."[22]

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"I voted yes. But don't take that to mean that I don't have grave concerns about the safety of this drug."

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Dr. Kowey also indicated that his vote was influenced by physicians on the committee when he explained "I said yes because I was listening to these guys who take care of these patients who would like to see this drug available. And I agree that they're a desperate lot of patients and they do need to have that drug, and I'd like to see it on the market. That's why I voted yes. But don't take that to mean that I don't have grave concerns about the safety of this drug, and if it's not communicated properly to the physicians, what's going to happen is you're going to run into the same withdrawal problems that you had with other drugs somebody mentioned earlier. So, I feel very strongly about that."[22]

Nevertheless, Drs. Califf and Kowey voted with the majority on the committee to recommend approval for the drug at the 2-milligram and 4-milligram doses. Their concerns were apparently well founded; the manufacturer withdrew its application for the drug before FDA announced a decision about approval.

Device Advisory Committee Members Explain Their Votes

Our analysis of the device advisory panel discussions focuses on the most extreme example first, the Ophthalmic Devices Advisory Panel, which recommended approval 88% of the time, usually unanimously.

Ophthalmic Devices Comments. As was the case in the drug advisory committees, the device transcripts indicate that members sometimes voted for approval despite serious concerns about the data or the product. For example, at the January 2002 meeting regarding a capsular tension ring for use in cataract surgery, Dr. Allen Ho voted for approval and summarized his views as follows: "Poor study, poor execution, flawed from the beginning, I think." [23] Similarly, in the May 2003 review of CrystaLens® (an artificial lens to correct visual impairment after cataract surgery), Dr. Arthur Bradley explained his vote and expressed his ambivalence as follows: "I think this is an exciting new product. I was disappointed with the quality of the data but I think it has demonstrated efficacy. Although somewhat marginally so. That's why I voted to approve." [24] The panel voted unanimously for approval.

The panel members' comments often show self-deprecating humor about their uncertainty, concerns, and peer pressure, but patients and consumers are not aware of the concerns that were expressed. If the FDA subsequently agrees with the recommendations and approves the product, patients and consumers assume that the product is safe and effective. Patients certainly would wonder, for example, why Dr. Joel Sugar recommended approval for the STAAR Implantable Contact Lens, if they heard him admit at the October 2003 panel meeting that although "I feel that the efficacy has been well demonstrated, the safety remains a concern." [25] They might not be reassured by Dr. Sugar's explanation that when he voted for approval, he hoped that longer term data would eventually indicate that the product is safe. They might be similarly surprised by the comments of Dr. Timothy McMahon, who admitted, "I've waffled through the day with regard to my vote for approvability" but explained he was convinced by "the reassurances that the Sponsor will look at the follow-up data in a responsible manner....And hopefully, this will turn out for the best for all of us."[25] Based on these concerns, it is fortunate for patients that, in one of its rare instances of not approving a medical device recommended by the advisory panel, the FDA did not approve this product.

In the November 2001 review of the Viewpoint CK system for the treatment of spherical hyperopia, Dr. Michael Grimmett said, "I unenthusiastically voted approvable with conditions, as I believe the procedure is reasonably safe, yet only marginally effective. I'm uncomfortable with the lack of stability of the procedure." He nevertheless voted for approval with the hope that labeling would help consumers "have an adequate chance of achieving the appropriate information in order to make an informed consent about this procedure."[26]

Similarly, at the February 2004 meeting regarding the ARTISAN® Intraocular Lens, Dr. Richard Casey indicated his willingness to vote for approval on the basis of wishful thinking: "While the data may not have been conclusive, I think certainly the trend was that it probably is efficacious and probably is safe." [27]

The Ophthalmic Devices Panel approved every device it reviewed during the last six years of our analysis, but even before that uninterrupted approval pattern started in the summer of 1999, individual members described surprisingly low standards for approval in their panel discussions. For example, for the February 1998 review of the Kremer LASIK device, Dr. Janice Jurkus explained that she voted for approval "because I did not see from the data that this was totally unsafe or totally ineffective." [28]

Radiological Devices Comments. Other device panels were similarly willing to vote for products that they recognized as questionable. One of the many examples is the December 2002 Radiological Devices Panel meeting assessing a device for thermal imaging for breast biopsies. Dr. Geoffrey Ibbott voted for approval. When the motion failed, he voted against approval, stating, "Well, I voted in favor of the first motion, but, like Dr. Tripuraneni, I'm quite comfortable with the approval of the second motion [against approval]."[29]

Obstetrics and Gynecology Devices Panel Comments. It is not unusual for individual members to be outspoken in their criticisms and yet consistently vote for approval. For example, in January 2001, the Obstetrics and Gynecology Devices Panel unanimously recommended approval for the FirstOption® Uterine Cryoblation Therapy System for treating abnormal uterine bleeding. There were strong concerns about the device, however, and Dr. Michael Diamond suggested the need for careful post-market surveillance. When challenged by other panel members that the risks of the product were not unique, Dr. Diamond explained, "Well, the difference between this device and the other ones ... [is] we haven't had a 25% or higher failure rate with a device as part of the clinical trial, which we do have here."[30] Despite these strongly worded concerns, Dr. Diamond voted for approval.

Similarly, in the same panel's review of an endometrial ablation system in June 2003, Dr. Diamond recommended that the medical device be approved without conditions despite "recognizing all the things that we have talked about and the nine questions we went through, which to me seem like we have pretty unanimous thoughts throughout them of how they needed to be modified or addressed." [31] In response to the suggestion from others on the panel that those modifications and concerns should be specified as conditions for approval, Dr. Diamond agreed.

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"What happens if, at the end of two years, the [Caesarean] section rate has doubled... and we say, 'My God, we made a terrible mistake approving this device?'"

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At the same panel's review of a fetal heart monitoring system in June 2005, Dr. Jay Iams opined that the company should be required to study if its device increased the Caesarean-section rate among women who used it. Dr. Julian Parer asked, "What happens if, at the end of two years, the [Caesarean] section rate has doubled, the rate of acidemia has tripled and we say, 'My God, we made a terrible mistake approving this device?' What option do we have?" [32] An FDA official candidly explained that "theoretically, FDA can withdraw PMA approval. In practice, that virtually never happens." Nevertheless, Dr. Parer and everyone else on the panel voted to approve the product.

Immunology Devices Comments. The Immunology Devices Advisory Panel considered no new devices between 1999 and 2004, but in 2005 it met to review the AlzheimAlert® test, a laboratory assay designed to measure proteins in urine specimens of patients with suspected Alzheimer's disease. The panel recommended against approval, but the two doctors who voted for approval indicated reasons that were not consistent with the FDA stated standard of proven safety and efficacy. For example, Dr. Oscar Lopez explained his support because "as a neurologist, and as somebody who works in the field of dementia, I believe that anything that increases awareness of the disease is positive and is important. So I think that would be very important to have something in the community... to have a tool that can increase their awareness of the disease. The problem that I have with the study is that it's not — I'm not convinced that it works in Alzheimer's disease."[33] Dr. Terrance Lichtor, a neurosurgeon who also voted in support of approval, stated, "It's not really identifying patients with Alzheimer's disease. It's more ... help and management of patients with dementia who do not have Alzheimer's disease. And that's more of what I see. But I feel that this test does add some information, and only time will tell whether or not this will pan out to be helpful." This was an opportunity for FDA officials on the panel to clarify the criteria for approval, but they remained silent.

Microbiology Devices Comments. At the March 2002 Microbiology Devices Advisory Panel meeting review of an HPV DNA test, panel members disagreed about the conditions for approval but voted for approval with those conditions anyway. For example, Dr. George Birdsong stated, "I'm going to say yes. I'm mixed on that one actually."[34] and Dr. Frederick Nolte was even blunter, "I voted in favor of the resolution. I guess I'm learning how to play politics ... but I think basically the test has value."

Approval Recommendations

Of the 50 drug advisory committee voting sessions in the study, 38 (76%) resulted in a recommendation for approval of the drug, not counting the one tie vote. Of those 50 voting sessions, 27 (54%) ended in unanimous votes, with 25 (93%) of those unanimous votes recommending approval. Overall, 50% of the time the drug advisory committees unanimously recommended approval of the drug application.

Of the 39 medical device panel voting sessions surveyed, 32 (82%) voted to recommend approval of the device. Of those 39 sessions, 26 (81%) of the votes were unanimous, with 24 (92%) of those unanimous votes recommending approval. Overall, the majority (62%) of the medical device advisory panels unanimously recommended approval of the device under consideration.

The next section of this report provides the specific data on voting patterns for each drug and device advisory committee.

Drug Approval Recommendations

Each of the drug advisory committees in the analysis recommended approval at least half the time. The percentage of drugs that were recommended for approval ranged from 50% for reproductive health drugs to 100% for arthritis drugs. The percentage of individual votes cast to recommend approval ranged from 50% for reproductive drugs to 98% for arthritis drugs.

The Arthritis Drugs Advisory Committee also was most likely to recommend approval unanimously: eight (89%) of the nine committee votes recommending approval between 1998 and 2005 were unanimous.

While 76% of 50 drug committee voting sessions recommended approval, 396 (75%) of the 527 votes cast by committee members were for approval.
Of the 11 drugs that drug advisory committees voted against between 1998 and 2005 (not including the one tie vote), the FDA subsequently approved five (45%) of them as of July 2006, including two that were rejected by the Dermatologic and Ophthalmic Advisory Committee (Cyclosporine, rejected 1-5 and Methyl Aminole, rejected 2-9), two rejected by the Gastrointestinal Advisory Committee (Zelmac®, rejected 1-7 and Serostim®, rejected 3-6), and one rejected 4-13 by the Antiviral Advisory Committee (Relenza®).

Of the 38 drugs recommended for approval by the drug advisory committees, all were approved except one drug whose application was withdrawn before FDA made its decision, as described previously in this report.

It is notable that although the drug advisory committees rarely rejected applications, the FDA was nine times more likely to follow the recommendations for approval than those against approval. This is surprising, since one might assume that the few drugs that were rejected must have particularly great risks or particularly poor safety and efficacy data. The fact that the FDA was so willing to overturn those recommendations adds to the impression that the FDA committee meetings are intended primarily as a mechanism for drug approval rather than for close scrutiny regarding whether approval is appropriate.

The voting patterns for specific drug advisory committees are presented below.

Antiviral Drugs. There were 98 Antiviral Drugs Advisory Committee members who cast 215 votes, 172 of which (80%) were for approval. Voting on 18 products, they recommended approval for 15 (83%), and 11 of these approval decisions (73%) were unanimous.

Of 36 committee members who voted for more than one product (a maximum of eight products), 13 (36%) always voted for approval. The more active members were less likely to vote for approval every time: of 19 who voted at least four times, only two (11%) always recommended approval.

Arthritis Drugs. Of all the drug and device committees in the study, the Arthritis Drugs Advisory Committee members were the most likely to

recommend approval. Its 33 committee members cast 83 votes for new drugs or new indications, 81 of which (98%) were for approval. They voted on seven drugs, two of which they voted on separately for two different indications. All nine (100%) votes were for approval, and they recommended approval for eight of the nine (89%) unanimously.

Since almost all the committee members voted for approval every time, it is not possible to distinguish among committee members who voted for or against approval.

Although our analysis did not examine conflicts of interest, it is notable that the conflicts of interest among members of this advisory committee have been scrutinized in an article published in the *Journal of the American Medical Association* in 2006. The authors reported, for example, that at a 2005 advisory committee meeting to evaluate the risks of Cox-2 inhibitor pain medication, 93% of the votes cast by members who had received consulting fees from at least one of the drug makers favored the drugs, compared with 55% of the votes by individuals without conflicts.[3] Since our report only analyzes roll call votes for products being considered for approval for the first time or for a new indication, we did not analyze the votes from that 2005 advisory committee meeting. However, the substantial number of Arthritis Drugs Advisory Committee members with financial ties to manufacturers certainly could help explain the extremely consistent pattern of support for approval for almost all the products this committee reviewed since 1998. Based on the voting patterns for that committee, it is likely that if several committee members vote for approval for any drug, the remaining committee members will vote the same way.

Dermatologic and Ophthalmic Drugs. There were 44 Dermatologic and Ophthalmic Drugs Advisory Committee members who cast 69 votes, 40 of which (58%) were for approval. They voted on eight products, and recommended five (63%) for approval. Two of those (40%) were unanimous. The votes against approval were not unanimous.

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93% of the votes cast by members who had received consulting fees from at least one of the drug makers favored the drugs.

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Of 17 committee members who voted for more than one product (six was the maximum), only five (29%) always voted for approval. Only three voted at least four times, none of whom always voted for approval.

Gastrointestinal Drugs. There were 44 Gastrointestinal Drugs Advisory Committee members who cast 62 votes, 43 of which (69%) were for approval. They voted on six products, and recommended four (67%) for approval. Two (50%) of these votes were unanimous. The votes against approval were not unanimous.

Of 16 committee members who voted for more than one product (three was the maximum), five members (31%) always voted for approval.

Pulmonary and Allergy Drugs. There were 38 Pulmonary and Allergy Drugs Advisory Committee members who cast 58 votes, 40 of which (69%) were for approval. They voted on five products, three (60%) of which they recommended for approval, and two (67%) of the three were unanimous. The votes against approval were not unanimous.

Of 10 committee members who voted for more than one product (four was the maximum), four (40%) always voted for approval. Of three who voted at least four times, only one (33%) always voted for approval.

Reproductive Health Drugs. There were 28 Reproductive Health Drugs Advisory Committee members who cast 40 votes, 20 of which (50%) were for approval. They voted on only three products, one of which was voted on separately for two different dosage levels. Committee members recommended approval of

the one drug at both dosage levels, thereby recommending approval of two (50%) of the four indications but only one (33%) of the three drugs. None of the votes for approval were unanimous, although one of the votes against was unanimous.

Of 12 committee members who voted twice, eight (67%) voted for approval both times. None of the committee members voted more than twice.

The small number of advisory committee meetings and the diversity of votes reflect substantial controversy involving the membership of this advisory committee, which in recent years included Dr. David Hager, a physician whose outspoken ideological opposition to some reproductive drugs has generated opposition to his membership on this committee.[35]

Device Approval Recommendations

All of the medical device advisory panels in our analysis recommended approval most of the time. The number of products that were recommended for approval ranged from 67% for microbiology devices to 88% for ophthalmic devices. The number of panel member votes cast to recommend approval ranged from 57% for microbiology devices to 91% for radiological devices. The microbiology panel was the only one where less than three-quarters of the products were recommended for approval or where less than three-quarters of the votes were in favor of approval.

Three of the five randomly selected device panels — the Radiological Devices Panel, the Immunology Devices Panel and the Microbiology Devices Panel — were always unanimous in their support for approval. The Radiological Devices Panel was most likely to recommend approval unanimously whenever they voted: six of the seven devices it reviewed between 1998 and 2005 (88%) were unanimously recommended.

While 82% of the 39 devices were recommended for approval, 272 of 339 individual device panel members' votes (80%) supported approval.

The FDA subsequently approved 30 (94%) of the 32 devices recommended by the advisory panels. However, the FDA also approved 43% of the devices that the panel voted should not be approved.

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Three of the five randomly selected device panels — the Radiological Devices Panel, the Immunology Devices Panel and the Microbiology Devices Panel — were always unanimous in their support for approval.

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Immunology Devices. There were 21 panel members who cast 29 votes, 24 of which (83%) were for approval. They voted on four products, three (75%) of which they recommended for approval, and all approvals were unanimous.

Only four of the panel members voted for more than one product (three was the maximum), but all (100%) always voted for approval.

Microbiology Devices. The Microbiology Devices Panel members were the least likely to recommend approval, although even they recommended approval most of the time. The 12 panel members cast 21 votes, 12 of which (57%) were for approval. They voted on three products, two (67%) of which they recommended for approval, and one (50%) of which they recommended unanimously.

Experience seemed to encourage panel members to vote against approval; panel members who participated in more panel meetings were more discriminating in their voting. Six of the panel members voted for more than one product (three was the maximum), and none of them always voted for approval.

Obstetric and Gynecological Devices. There were 43 panel members who cast 87 votes, 66 of which (76%) were for approval. They voted on nine products, seven (78%) of which they recommended for approval, and five of the approvals (71%) were unanimous.

Of 23 panel members who voted for more than one product (maximum of six), nine (39%) always voted for

approval. Of four who voted at least four times, two (50%) always voted yes. The most active members of the panel always voted for approval (five times out of five, and six times out of six).

Ophthalmic Devices. Thirty-two Ophthalmic Devices Advisory Panel members cast 157 votes, 129 of which (82%) were for approval. They voted on 16 products, 14 (88%) of which they recommended for approval, and 10 (71%) of these were unanimous. This panel has not rejected any devices since July 1999.

Of 25 panel members who voted at least twice (with a maximum of 12 votes), only five (20%) always voted for approval. Of 20 who voted at least four times, only three (15%) always voted for approval.

Radiological Devices. There were 38 Radiological Devices Advisory Panel members who cast 45 votes, 41 of which (91%) were for approval. They voted on seven products, six (86%) of which they recommended for approval, and all (100%) were unanimous.

Of 10 panel members who voted for more than one product (five was the maximum), four (40%) always voted for approval. Of three who voted for at least four products, only one (33%) always voted for approval.

Labeling, Conditions of Approval, and FDA Approval Decisions

When committee members vote for approval, they often include caveats as a condition of approval or specify the risks of the product that should be included on the label. They also may ask that the label describe restrictions in the use of the product, for example, whether it is intended for individuals in certain age groups and whether the product is proven safe for pregnant women.

The advisory committee meeting transcripts indicate that when committee members have concerns about the safety of a product, they often vote for approval but also vote for conditions or restrictions that reflect those concerns. In fact, all but one of the approval votes for the device panel meetings were votes in favor of "approval with conditions." The conditions were sometimes numerous and quite burdensome, including studies to be conducted after the product was approved to examine long-term safety or efficacy. While providing clear guidance to the FDA about committee members' concerns, conditions of approval may serve another function: a compromise that helps persuade reluctant advisory committee members to vote for approval, so that they do not require better data to prove the product is safe or effective before approval is granted.

For example, at the June 2004 meeting of the Obstetrics and Gynecology Devices Advisory Panel that reviewed a high intensity ultrasound system called ExAblate 2000® for uterine fibroids, Dr. Grace Janik stated, "there are a number of us that have insecurities if efficacy is truly demonstrated here" and recommended that the company do more research before the product is approved.[36] She was told that a pre-market study was "not really germane" to the discussion because they were voting on conditions of approval; if a pre-market study was needed, then the product should not be approved. Another panel member asked "can we be at a point in discussing conditions if we haven't decided approval or disapproval?" and was told by the panel chair, Dr. Kenneth Noller, "Yes, that's what we do." At that point, two panel members suggested that Dr. Janik propose the study as a post-market study instead of a pre-market study, which Dr. Janik declined to do. Dr. Janik subsequently voted against approval, but the product was recommended with seven conditions of approval, on an 8-5 vote.

The advisory panel members recommended conditions that they considered essential for approval. However, the only one of those seven conditions of approval that was specified in the FDA's letter to the company was a post-approval 3-year study, which would include more African-American women.[37] African-American women are at much greater risk of uterine fibroids than white women, but the product — used for the treatment of uterine fibroids — was approved despite African-American women being "under-represented in the pivotal study."[vi]

Although advisory panels often spend considerable time voting on conditions of approval in an effort to provide essential safeguards, an analysis of the final FDA approval letters indicate that most conditions of approval specified by advisory panels were not imposed on the companies.[vii] Another example of what happens

to these conditions is the approval decision regarding CrystaLens®, the implantable intraocular lens that was recommended for approval with 14 conditions at a May 2003 Ophthalmic Devices Advisory Panel meeting. The FDA meeting transcript indicates that the panel agreed to 14 often very technical conditions of approval, but most of those conditions were not imposed on the company in the letter of approval. Instead, the FDA informed the company that they must register all patients "in a data base to be maintained indefinitely, or until the applicant is otherwise notified."[38] The FDA also specified that any "warranty statements must be truthful, accurate, and not misleading."

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The panel agreed to 14 often very technical conditions of approval, but most of those conditions were not imposed on the company in the letter of approval. Instead, the FDA informed the company that they must register all patients.

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The data suggest that most conditions recommended by advisory panels are not included in the final FDA decision. A separate issue is whether the conditions are enforced. That will be dicussed in the next section of this report.

In addition to changing and deleting many of the recommended conditions of approval, the FDA can make approval decisions that are different from the recommendations of their advisory committees. For the new medical products or new indications reviewed by advisory committees from 1998 through 2005, 79% were recommended for approval, and even more — at least 88% — of all those reviewed were approved by the FDA. The percentage of approvals is even higher than the percentage recommended for approval because while 95% of those recommended for approval were subsequently approved, 44% of those that were not recommended were approved anyway. The chance of a "non-approval recommendation" being overturned by the FDA in favor of approval was 45% for drugs and 43% for devices. In fact, the FDA was nine times as likely to approve drugs and devices that were recommended for non-approval than they were to reject drugs and devices that were recommended for approval. These numbers are underestimates because there are medical products that were reviewed in this study that may yet be approved by the FDA, particularly those reviewed in 2005.

[vi] If the health of African-American women was considered important, these women should have been studied more carefully before the product was approved.

[vii] The specific conditions of approval are included in the letter to the company. A "Conditions of Approval" document accompanies the letter; that document includes general instructions about post-approval reports and adverse reaction and device defect reporting, as well as the need for a PMA supplement if the company makes substantial changes to the product.

Overall, the findings suggest that when the FDA schedules most of its advisory committee meetings, the outcome is almost certainly going to be FDA approval for the product under review. The outcome is less certain for drugs than devices, and much less certain for some committees than others.

There is no doubt that FDA advisory committee meetings focus not only on an up or down vote for approval, but also on the labeling and other conditions of approval, such as delineating post-market research and surveillance. However, if these conditions are a primary purpose of the advisory committee meetings, it is surprising that the conditions are so frequently omitted or drastically revised in the final approval decisions.

Are the conditions of approval that the panels recommend feasible and enforceable? FDA officials rarely provide information during the meeting about the limitations of FDA authority to mandate certain types of restrictions or to enforce post-market research or surveillance. As a result, the conditions of approval may be unrealistic.

On the other hand, even when the FDA reduced the conditions to ones they considered essential and enforceable during the eight years of our study, the FDA often failed to monitor or enforce those conditions. Scientists at FDA's Center for Devices and Radiological Health could not find information on most (58%) of the Condition of Approval Studies required as part of the PMAs approved between 1998 and 2000.[39] FDA's record for enforcing post-market drug commitments is similarly lax. According to a report released by the FDA in March 2006, drug companies had failed to initiate 65% of required post-market study commitments.[40] Only 14% of open post-market study commitments had been submitted.

Numerous official documents and quotations by FDA officials praise the advisory committee process as an objective, scientific review by independent, outside experts who are reviewing the most controversial and cutting-edge medical products to determine whether they should be approved and, if so, under what conditions. Based on the FDA's official description, the advisory committee meetings are viewed as an important part of the process and committee recommendations are assumed to be influential, with media reminding readers that "the FDA does not have to follow the recommendations of their advisory committees, but they do so 90% of the time."[41]

The results of this study contradict that public image for many of the committees. While it is impossible to say what percentage of drugs and devices would be recommended for approval under ideal conditions with careful scientific scrutiny, the findings of this report are worrisome. The percentage of approval recommendations is very high, the percentage of unanimous approvals is very high, and advisory committee members are regularly admitting that they are voting for approval despite serious misgivings about safety or efficacy. Many committees are relying on post-market studies when they consider the pre-market studies inadequate, but the post-market track record is very poor for drugs and devices.

The drug advisory committees have less extreme records of recommending approval than the device advisory panels. Although all drug advisory committees recommended approval at least half the time, only two recommended approval more than two-thirds of the time. However, those two committees, reviewing antiviral drugs and arthritis drugs, reviewed most of the new drugs from 1998-2005 for the six committees studied.

In contrast, all medical device panels recommended approval at least two-thirds of the time, and four of the five recommended approval at least three-quarters of the time, frequently unanimously.

For several of the committees in this study, the vast majority of prescription drugs and medical devices will be approved, apparently regardless of the concerns of committee members. The conditions of approval that are recommended will rarely be imposed. Moreover, although the FDA follows advisory committees' recommendations for approval 95% of the time, they are half as likely to follow recommendations for non-approval. This suggests that advisory committee votes for approval reflect pressure for approval coming from the FDA. It seems likely that for many of these advisory committees, staff time and resources could be better spent on a better advisory committee process.

Conflicts of Interest and Biased Experts

There are many possible reasons why the current advisory committees recommend approval most of the time, even when members have substantial concerns about safety or efficacy. The possible explanation that has attracted the most attention in recent years — in the media, in Congress, and among consumer advocates — is the existence of financial conflicts of interest among FDA committee members. For example, in an analysis of advisory committee meetings that was published in the *Journal of the American Medical Association (JAMA)*, the FDA reported at least one voting committee member with a financial conflict of interest at more than 80% of the meetings that reviewed specific products, and 22% of the conflicts were with the company whose product was under review.[4] Committee members with financial ties to a competitor were even more supportive of approval than those with financial ties to the company making the product. That surprising finding was highlighted by the FDA in a response to the article, claiming that since committee members were voting in favor of competitors' products, the financial conflicts must not be biasing the votes.[42]

The study presented in this report differs from previous FDA advisory committee studies in many important ways; for example, the *USA Today* study and the *JAMA* study analyzed conflicts of interest. Both of those studies analyzed all drug advisory committee meetings for several years, whereas our study analyzed a random sample of drug and device advisory committees for more years but included only new drug or device approvals, and our study analyzed only the votes regarding approval or non-approval, not other votes pertaining to safety, efficacy, or labeling. Equally important, the *JAMA* study excluded from analysis any votes that were unanimous, since it was interested only in explaining voting differences on each committee.

The FDA conducted its own survey to examine the views of advisory committee members and individuals attending 11 advisory committee meetings in 2003.[43] The results were quite favorable about the advisory committee process at the meetings attended, although many respondents expressed concerns about conflicts of interest and most disagreed with the statement "The meetings do not favor certain people or organizations above others." The usefulness of the data are limited, however, because the survey response rate was only 21%. Moreover, 82% of those who participated in the FDA survey stated that they were paid to attend the advisory committee meeting, but the survey results did not specify whether they were paid by the company whose product was under review, by the federal government, or by other sources that might have influenced their views. Despite the substantial differences in methodology, the information from the previous studies has interesting implications for this report, and vice-versa. Since our findings indicate the tendency for committee members to come to consensus rather than vote their differences, the fact that so many committee members have financial ties to the companies involved could have an enormous impact, disproportionate to the specific numbers of committee members with such conflicts. In fact, just one or two committee members whose votes are influenced by their financial ties could easily influence the recommendations of their entire committee, even resulting in unanimous recommendations for approval. This would be especially likely if the person with the financial ties were to be very active in the committee discussion, since there is often considerable agreement in the discussions. It would be even more influential if an individual with financial ties to the company made the motion for approval, since unanimity follows those first votes most of the time, especially for medical devices.

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Commitee members vote "yes" even if it means changing the wording of the question so that they can do so in good conscience.

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Peer Pressure?

This study includes quotations from committee members whose votes seem inconsistent with their concerns about the safety or efficacy of the drug or medical device under review. These quotations are not representative of the entire discussion, but they clearly illustrate the pressures that committee members describe to conform to their col-

leagues or to be able to vote "yes" even if it means changing the wording of the question so that they can do so in good conscience. Their candor suggests that they would welcome guidance from FDA officials to make sure their recommendations are appropriate.

We also found examples where committee members directly tried to influence the views or votes of other committee members. One especially telling example is when a committee member wanted the panel to require an additional study be completed before approval was granted, to make sure the product was effective. She was then urged by other committee members to instead ask that the study be recommended as a post-market study. That compromise would enable panel members to vote for approval and also ask for the study, but with no guarantee that the study would be conducted and the results would indicate that the product was effective. The explicit pressure to change her mind is an example of how the process pushes toward the most common endpoint: approval with conditions.

Most members of FDA committees serve for several years and are sometimes invited to temporarily serve on other committees as well, while other individuals are repeatedly invited to serve as consultants with temporary voting privileges. Based on those patterns of individuals participating on several committees, FDA officials who decide whom to invite often know in advance (or could easily find out) if those committee members tend to vote for or against approval. It is therefore possible that many committees are "stacked decks," with approval virtually inevitable. It is not possible to tell from this study whether "stacked deck" committees that always vote for approval were intentionally selected to achieve that outcome, or if that outcome was not intentional. However, a 2006 survey of FDA scientists by the Union of Concerned Scientists (UCS) reported that such manipulation was sometimes intentional.[44]

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There is no indication that FDA officials are unhappy with the overwhelming approval patterns of most of these committee votes, or the conditions that are recommended.

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FDA Advice: Part of the Solution or Part of the Problem?

The UCS 2006 survey of FDA scientists and an internal FDA survey quoted by UCS suggest that there is pressure within the agency to stifle risk information and to approve new medical products despite safety concerns. Such pressures could influence the advisory committee recommendations, since the committees depend on the FDA scientists for objective analyses of the data. The wording of the questions that FDA prepares for committee members to vote on also influences whether the votes will support approval or not. Certainly, there is no indication that FDA officials are unhappy with the overwhelming approval patterns of most of these committee votes, or the conditions that are recommended. In fact, committees that vote for approval the greatest percentage of the time tend to meet more often than committees where the votes are less likely to be for approval.

The transcripts indicate that when committee members expressed their intention to vote for approval despite lack of safety or efficacy data, FDA officials did not urge committee members to make careful recommendations based on research evidence. An FDA official might read rather lengthy boilerplate instructions that include the definitions of safety and effectiveness, but FDA officials almost never respond to drug or device committee members' often lax interpretations of approval criteria. An FDA official's one clear reminder that committee members should vote for approval only if a product was safe and effective, at an Arthritis Drugs Advisory Committee meeting in 2001 that was quoted earlier in this report, stands out because it is so unusual. Moreover, an Internet search on the FDA Web site indicates that the FDA staff involved, Dr. Jay Siegel, has not participated in any FDA advisory committee meetings to review new medical products or new indications since that 2001 meeting.

Perhaps FDA officials generally avoid such comments because they do not want to unduly influence the advisory committee, which is intended to be an independent voice in the FDA approval process. If that is the reason for their silence, however, it is misguided. As shown in the section of this report quoting committee members, many are quite outspoken about their concerns and about their interpretation of the criteria for approval being less than clear

evidence of safety or effectiveness. All committee meetings include FDA staff at the dais with the committee members, with numerous FDA officials in the audience as well. When committee members express their willingness to vote for approval despite strong concerns about whether the product is safe or effective, their comments are generally met with silence from FDA staff and officials. This is likely to be interpreted as FDA agreement with their statements.

The *pro forma* recitation of boiler-plate instructions does not seem to provide useful guidance for FDA committee members during the course of their deliberations. Moreover, the silence of FDA staff and officials when committee members indicate their intention to vote in ways that are inconsistent with their stated views sends the message that whatever assumptions the committee members express about the decision-making process are correct. Similarly, the conditions of approval that are discussed and voted on during committee meetings attract very little guidance from FDA officials who are at the dais or in the room. Committee members propose conditions that in some cases would not be seriously considered by the FDA, or could not be enforced by the FDA, but the proposed conditions receive little feedback from the agency while these discussions and votes are underway. Instead, FDA officials simply do not impose most of them when final decisions are made.

Overall, FDA officials showed remarkably little interest in providing guidance to advisory committee members during the eight years of committee meetings analyzed in this report. Certainly, this gives the impression that FDA officials are satisfied with the current process, one where committee members intentionally or unintentionally move toward a consensus that often seems inconsistent with their differing views or perspectives in making decisions that may have life-or-death consequences for millions of Americans.

RECOMMENDATIONS

Regardless of the reasons, many of FDA's advisory committees seem destined to recommend approval almost every time they meet. Moreover, even when a very strong majority recommends "non-approval," FDA officials often approve the product anyway.

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Many of FDA's advisory committees seem destined to recommend approval almost every time they meet. Moreover, even when a very strong majority recommend "non-approval," FDA officials may approve the product anyway.

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In recent years, this pattern of approving medical products in spite of serious concerns has resulted in a large number of well-publicized cases when FDA-approved products were found to have high risks of death and serious injury. Whether the products are voluntarily or forcibly removed from the market or temporarily recalled, these situations undermine the credibility of the FDA and the trust of the American public. If the FDA wants to restore confidence in the FDA and restore the independence that FDA advisory committees were intended to provide, it is essential that the FDA make changes in the policies and process governing their advisory committees. The following recommendations are based on the assumption that the Congress and the FDA are committed to that end.

1. **The FDA should stop granting conflict-of-interest waivers for committee members, except under very restricted conditions.**

Research on conflicts of interest among FDA advisory committee members has focused on the votes of members with conflicts of interest. As long as voting members with conflicts of interest did not outnumber the other voting members, it was assumed that the conflicts did not matter. However, the findings in this report clearly show that one or more members on each advisory committee can easily sway the entire committee's vote.

Committee members with financial conflicts of interest may have more expertise regarding a new medical product, but research indicates that they are also more likely to be more supportive of FDA approval. Their expertise is likely to also make them more outspoken, leaders on the committee rather than followers. The role of committee members with financial ties to the product is illustrated by the Arthritis Drugs Advisory Committee, which has included many members with financial ties to the products under review, and also shows an overwhelming pattern of voting in favor of approval of almost every medication that comes before it. For example, even after numerous reports of deaths linked to Vioxx®, many committee members continued to defend its use despite the availability of many safer, less expensive alternatives.[45]

In July 2006, the FDA announced its intention to improve its advisory panel process by making information about conflicts of interest more transparent. Although transparency is useful, there is no evidence that transparency would reduce the likelihood of biased advisory panel members influencing FDA approval decisions. If panel members are aware, for example, that a colleague on the panel has served as a generously paid consultant to the company whose product is under consideration, that might make them more skeptical of the consultant/committee member's comments. However, it would be unlikely to have much impact on the consultant/committee member's influence on voting, given the collegial atmosphere of advisory committee deliberations. The study findings indicate that if the consultant/committee member is very enthusiastic about a product, that enthusiasm will be contagious, and if he or she is the first to recommend approval, the product would likely be recommended for approval, probably unanimously.

2. **The FDA should provide explicit and specific oral guidance whenever needed during advisory committee meetings regarding appropriate criteria for safety and effectiveness, and appropriate criteria for conditions of approval.**

The Center for Devices and Radiological Health requires only a "reasonable assurance" of safety and efficacy rather than proof, and panel members interpret this to mean that neither safety nor effectiveness is required. In recent years, FDA safety criteria regarding drugs and devices have increasingly emphasized the need to manage risk, rather than a more traditional concept of safety.[46] The message has been heard loud and clear by committee members, some of whom explicitly indicate that they believe the FDA standard for approval does not require a product to be proven either safe or effective. The widely shared acknowledgement that all products have adverse reactions for some individuals under some circumstances has been used to justify ignoring concerns about potentially serious risks for large numbers of patients. This seems to be especially true for committees that virtually always vote for approval despite strong concerns. Meanwhile, advisory committee members often support approval on the condition of post-market research and surveillance, apparently not informed that FDA officials have acknowledged that the FDA lacked the staff to review and analyze adverse reaction reports in a timely manner [47] and that required post-market studies are not monitored by FDA and are rarely completed.[39, 40]

Our review of meeting transcripts indicates a clear problem in how safety and efficacy criteria are defined. The FDA must address that issue directly during meeting deliberations."

3. The FDA should expect more from advisory committee members, and then be more responsive to their concerns.

The FDA should rely on the advisory committees for impressive expertise and sound advice. Their votes for or against approval should be discriminating and their recommendations about labeling and conditions of approval should be credible, useful, and enforceable. Based on the data in this study, the voting by some advisory committees does not appear to be sufficiently discriminating, and yet the few products that are not recommended for approval are often approved by the FDA anyway. The recommended conditions of approval are often not imposed. This suggests that the advisory committees are not providing advice that is being well-used by the FDA. However, the study results do not indicate whether the FDA is satisfied with the status quo, where advisory committee votes can be used to justify approval decisions, and members' concerns are frequently ignored.

Serving on FDA advisory committees is an honor and privilege. The FDA should expect members to be well prepared at the meetings, and to have carefully reviewed the data and materials before the meeting. If it is necessary to provide more generous honoraria to ensure that, the FDA should do so. If scientific scrutiny is the goal, the FDA needs to do a better job of emphasizing the importance of careful review of data. The process needs to be changed so that committee members are encouraged to ask FDA staff for assistance in understanding data before or during an advisory committee meeting. If committee members lack the expertise to understand statistical analyses, training should be offered to help with that prior to the meetings. In addition, the FDA should provide training or guidance regarding the limitations of conditions of approval, particularly those involving labeling and post-market surveillance and data collection and analysis.

A review of meeting transcripts makes it clear that many committees include members who are not fully participating. When it is obvious that certain panel members are not familiar with the materials that they were supposed to have reviewed, did not understand the essential findings, or are not fully engaged in the meeting presentations or discussions, the FDA should terminate their participation in that meeting or future committee meetings.

At the same time, the FDA should provide comprehensive, accurate information about the shortcomings of the research for the product under consideration and the questions raised by FDA scientists reviewing the data. The FDA written memorandum provided to advisory committee members should include a candid assessment of safety and effectiveness that accurately reflects the views of FDA scientists. These views should not be censored and should be explicitly articulated as part of the FDA's oral presentation at the meetings. If essential scientific issues are not raised during committee discussions, FDA scientists or officials at the meeting should raise them in the form of questions or reminders to committee members.

If implemented, these recommendations would result in more objective scientific scrutiny by advisory committee members, an atmosphere that emphasizes careful, research-based deliberation, and committee recommendations that truly provide credible, independent expertise and advice for the benefit of the American public.

REFERENCES

FDA Advisory Committees: Does Approval Mean Safety?

1 Getting Outside Advice for 'Close Calls", January 1995 FDA Consumer special report. http://www.fda.gov/fdac/special/newdrug/advice.html Accessed August 14, 2006

2 Sherman LA. Looking Through a Window of the Food and Drug Administration: FDA's Advisory Committee System, *Preclinica*. Volume 2, No. 2 March/April 2004 http://www.preclinica.com/pdf/articles/sherman_2-2.pdf

3 Advisory Committees: Critical to the FDA's Product Review Process, *FDA Consumer*, January-February 2004, FDA 04-1334C http://www.fda.gov/fdac/special/testtubetopatient/advisory.html

4 Lurie P, Almeida CM, Stine N, Stine A.R. & Wolfe, S.M. Financial Conflict of Interest Disclosure and Voting Patterns at Food and Drug Administration Drug Advisory Committee Meetings, *Journal of the American Medical Association*. 2006, 295: 1921-1928.

5 Newburger AE. Cosmetic Medical Devices and Their FDA Regulation, *Archives in Dermatology* 2006: *142*: 225-228.

6 Cauchon D. FDA Advisers Tied To Industry. *USA Today*, September 25, 2000, pg 1A.

7 FDA Inspection Report of Bausch & Lomb, Inc. Available at http://www.fda.gov/ora/frequent/483s/1032500_baushlomb/baush_lomb_483.pdf, accessed August 15, 2006

8 FDA Arthritis Drug Advisory Committee Meeting Transcript, August 7, 1998, pg 231. Available at http://www.fda.gov/ohrms/dockets/ac/cder98t.htm, accessed November 29, 2005

9 FDA Arthritis Drug Advisory Committee Meeting Transcript, March 5, 2003, pgs 417-418. Available at http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3930T2.pdf, accessed August 10, 2006

10 FDA Consumer Information Sheet: Leflunomide (marketed as Arava), http://www.fda.gov/cder/consumerinfo/druginfo/Arava.HTM, accessed August 8, 2006

11 FDA Arthritis Drug Advisory Committee Meeting Transcript, August 16, 2001, pgs 190-191. Available at http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3779t1.pdf, accessed August 14, 2006

12 FDA Arthritis Drug Advisory Committee Meeting Transcript, April 11, 2000, pg 162-164 Available at http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3608t1b.pdf, accessed August 16, 2006.

13 FDA Antiviral Drugs Advisory Committee Meeting Transcript, January 14 1998, pg 241. Available at http://www.fda.gov/ohrms/dockets/ac/cder98t.htm, accessed November 29, 2005

14 FDA Antiviral Drugs Advisory Committee Meeting Transcript, July 27, 1999, pg 265. Available at http://www.fda.gov/ohrms/dockets/ac/99/transcpt/3529t1c.pdf, accessed August 8, 2006

15 FDA Antiviral Drugs Advisory Committee Meeting Transcript, February 27, 2001, pg166. Available at http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3731r1_02.pdf, accessed August 14, 2006

16 FDA Dermatologic and Ophthalmic Drugs Advisory Committee Meeting Transcript, March 17, 2003, pg 245. Available at http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3929T1.pdf, accessed August 8, 2006

17 Letter from Suzanne Berkman, Regulatory Review Officer at the FDA, November 2, 2005. Available at http://www.wlf.org/upload/DDMwrnVitrase.pdf

18 FDA Gastrointestinal Drugs Advisory Committee Meeting Transcript, June 27, 2000, pg 214. Available at http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3627t2c.pdf, accessed August 8, 2006

19 FDA Gastrointestinal Drugs Advisory Committee Meeting Transcript, March 6, 2003, pg 243. Available at

http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3928T1.pdf, accessed August 8, 2006

[20] FDA Pulmonary-Allergy Drug Products Advisory Committee Meeting Transcript, September 5, 2003, pg 216. Available at http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3976T1.pdf , accessed August 4, 2006

[21] FDA Reproductive Drugs Advisory Committee Meeting Transcript, April 10, 2000 pgs 193-194. Available at http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3602t1b.pdf, accessed August 8, 2006

[22] FDA Reproductive Drugs Advisory Committee Meeting Transcript, April 10, 2000, pgs 221-223. Available at http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3602t1c.pdf, accessed August 8, 2006

[23] FDA Ophthalmic Devices Panel Meeting Transcript, January 17, 2002, pg 31. Available at http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3833t1_01.pdf, accessed August 4, 2006

[24] FDA Ophthalmic Devices Panel Meeting Transcript, May 23, 2003, pg 255. Available at http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3953t1.doc, accessed August 4, 2006

[25] FDA Ophthalmic Devices Panel Meeting Transcript, October 3, 2003, pgs 428-430. Available at http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3991t1-05.pdf, accessed August 4, 2006

[26] FDA Ophthalmic Devices Panel Meeting Transcript, November 30, 2001, pgs 218-219. Available at http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3806t1_03_Afternoon_Session.pdf, accessed August 4, 2006

[27] FDA Ophthalmic Devices Panel Meeting Transcript, February 5, 2004, pg 351. Available at http://www.fda.gov/ohrms/dockets/ac/04/transcripts/Pages%20from%204023t1-04.pdf, accessed August 4, 2006

[28] FDA Ophthalmic Devices Panel Meeting Transcript, February 13, 1998, pgs 169-170. Available at http://www.fda.gov/ohrms/dockets/ac/98/transcpt/3379t2.pdf, accessed August 4, 2006

[29] FDA Radiological Devices Panel Meeting, December 2, 2002, page 278. Available at http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3918t1-03.pdf , accessed August 21, 2006

[30] FDA Obstetrics and Gynecology Devices Panel Meeting Transcript, January 29, 2001, pg 207. Available at http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3686t1_03.pdf, accessed August 8, 2006

[31] FDA Obstetrics and Gynecology Devices Panel Meeting Transcript, June 10, 2003, page number not available. Available at http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3963t2.htm accessed August 8, 2006

[32] FDA Obstetrics and Gynecology Devices Panel Meeting Transcript, June 3, 2005, page number not available. Available at http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4150t1.htm, accessed August 8, 2006

[33] FDA Immunology Devices Panel Meeting Transcript, July 15, 2005, page number not available. Available at http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4163t1.htm, accessed August 8, 2006

[34] FDA Microbiology Devices Panel Meeting Transcript, March 8, 2002, pgs 251-257. Available at http://www.fda.gov/ohrms/dockets/ac/02/Transcripts/3846t2_03.pdf, accessed August 4, 2006

[35] Shorto R. "Contra-Contraception", *The New York Times*. May 7, 2006, Magazine; pg 48.

[36] FDA Obstetrics and Gynecology Devices Panel Meeting Transcript, June 3, 2004, pgs 331-332. Available at http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4046t1_04.pdf accessed August 17, 2006

[37] Letter from Donna-Bea Tillman, PhD, Director of Device Evaluation, FDA, to Robert Newman, InSightec – North America, October 22, 2004. Available at http://www.fda.gov/cdrh/pdf4/P040003a.pdf, accessed August 18, 2006

[38] Letter from Daniel Schultz, MD, Director of the Office of Device Evaluation, FDA, to Paul Kramsky, eyeonics, inc, November 14, 2003. Available at http://www.fda.gov/ohrms/dockets/dailys/04/jan04/011304/04m-0012-aav0001-02-approval-order-vol1.pdf

[39] Brown SL, Bezabeh S, Duggirala HJ. Center for Devices and Radiological Health, Condition of Approval Studies As a Postmarket Tool for PMA Approved Cohort 1998-2000 Final Report, March 18, 2005

[40] Report on the Performance of Drug and Biologics Firms in Conducting Postmarketing Commitment Studies, *Federal Register*, Vol. 71, No. 42, March 3, 2006, page 10979.

[41] Dembner A. "US keeps limits on implants". *Boston Globe*, January 9, 2004, http://www.boston.com/news/nation/articles/2004/01/09/us_keeps_limits_on_implants/, accessed August 18, 2006

[42] "Comment on Financial Conflict of Interest Disclosure and Voting Patterns at Food and Drug Administration Drug Advisory Committee Meetings", http://www.fda.gov/oc/advisory/analysis.html, accessed August 18, 2006

[43] McComas KA and Sherman LA. "Conflicts of Interest and FDA Advisory Committee Meetings: A Study of Public Attitudes and Opinions" http://www.fda.gov/oc/advisory/acstudy0904/JIFSANresearch.html, accessed August 18, 2006

[44] Union of Concerned Scientists FDA Survey: Essay Responses. Available at http://www.ucsusa.org/scientific_integrity/interference/fda-scientists-survey-summary.html, accessed on August 18, 2006.

[45] Berenson A. and Harris G. "10 Voters on Panel Backing Pain Pills Had Industry Ties". *The New York Times*, February 25, 2005, http://www.nytimes.com/2005/02/25/politics/25fda.html?ei=5088&en=ad0fd8db4df113e0&ex=1267074000&adxnnl=0&partner=rssnyt&adxnnlx=1155745825-kF+05zqs05ShxqiF5cqJDA&pagewanted=all&position=, accessed August 18, 2006

[46] See, for example CDER/CBER Risk Management Public Workshop, April 9-11, 2003, http://www.fda.gov/cder/meeting/riskManagement.htm, accessed August 19, 2006

[47] FDA Presentation to Consumer Groups, Washington D.C., on May 23, 2006

APPENDIX A

Center for Devices and Radiological Health Advisory Panel Process [a]

When considering new medical devices for market approval, the Food and Drug Administration (FDA) refers to an outside panel of experts, or an advisory committee, to review the safety and effectiveness of the product(s). The pre-market application (PMA) of the product, which outlines the product's description, intended use, and any clinical research on its safety, is reviewed during a public meeting. Then the advisory panel must submit a final report to the FDA that includes the committee's recommendation and the basis for such recommendation on the PMA.

Within 180 days of the date of filing of the PMA, the FDA will complete its review of the PMA and of the advisory committee's report and recommendation, and then the FDA submits its final decision. When none of the reasons that would deny its approval apply, the PMA receives an approval order. The FDA's approval announcement and summary of the product's safety and effectiveness are then made available to the public on its Web site, and any adverse effects of the device on human health are listed.

The FDA might instead issue an "approvable" letter to the applicant, which describes the information that the FDA requires to be provided or the conditions that the applicant is required to meet in order to obtain approval. The "Conditions of Approval" are the standard post-approval conditions imposed by the FDA and are applicable to all original PMAs and PMA supplements. For example, the applicant may have to agree to a post-approval study, restrictions on prescription use, or restrictions on the training of individuals who may use the device before approval. In general, as a condition of approval, the applicant agrees to abide by advertising and final printed labeling requirements and to submit adverse event reports, annual reports, and PMA supplements for changes. The applicant has three choices when met with an approvable letter: to amend the PMA as requested; to consider the decision as a denial of the PMA and to request administrative review; or to withdraw the PMA entirely.

In the event that a PMA does not meet FDA standards, the FDA will administer a "not-approvable" letter to the applicant that describes the deficiencies in the application. In many cases, the FDA is unable to reach an "approvable" decision due to a lack of significant information in the application. This decision informs the applicant what can be improved or changed to make the PMA approvable. Upon receiving the not-approvable letter, the applicant can choose one of the three actions mentioned earlier: to amend the PMA, to request administrative review, or to withdraw it.

Finally, the FDA may issue an order denying approval of a PMA after sending an approvable or not-approvable letter to the applicant. Such a decision is based on several factors. The PMA will not be approved if the application contains a false statement of material fact or if the labeling of the device does not comply with FDA requirements. Also, the PMA will be denied if an essential non-clinical laboratory study was not conducted in compliance with FDA regulations, or if the safety and rights of human subjects were not adequately protected during testing. Where practical, the denial order also will identify measures required to place the PMA in approvable form, and its contents are made available to the public on the FDA's Web site.

[a] Information from CDRH Device Advice for Industry Web site. Available at http://www.fda.gov/cdrh/devadvice/pma/review_process.html Accessed August 16, 2006

APPENDIX B

Center for Drug Evaluation and Research Advisory Committee Process

ACTION ON COMMITTEE RECOMMENDATIONS [a]

Advisory committees provide recommendations to the Agency on matters brought before them for consideration, but final decisions on such matters are made by the Agency. Section 505(n)(8) of the Act directs the FDA official responsible for the matter to notify affected persons of the Agency's decisions on advisory committee recommendations within 90 calendar days of the committee recommendation. As used in this guidance with respect to the clinical investigation of a drug or the approval for marketing of a drug, the FDA official responsible for the matter (i.e., the primary Agency decision maker) is the individual (generally a Division Director or Office Director) who has the authority to approve the application (see CDER MAPP 4634.1, CBER SOP 8405). To maintain consistency with FDA disclosure of information regulations (e.g., 21CFR Part 20 and §§ 312.130 and 314.430), "affected persons" with respect to advisory committee recommendations means the sponsors of clinical investigations and/or applicants for FDA approval of drug products on which an advisory committee has provided advice.

To implement this provision, the primary Agency decision maker should, within 90 calendar days of the committee recommendation, review the committee's recommendation and notify the affected persons of the status of FDA's decision on the matter. If no decision has been reached within this time frame, the primary Agency decision maker should notify the affected persons and indicate the reasons for no decision. The rationale for decisions and reasons for no decisions should be documented.

[a] Copied verbatim from Guidance for Industry, Advisory Committees: Implementing Section 120 of the Food and Drug Administration Modernization Act of 1997. October 1998

Drug Panels Votes Summary, 1998-2005

	Entire Panel							Votes by individual panel members		
Panel	Total panel votes on APPROVAL of NDA's	Total Panel Votes For APPROVAL of Drug	# of Unanimous votes	Panel votes for APPROVAL that were unanimous	% of Panel Votes for APPROVAL	% of ALL votes that were unanimous for APPROVAL		Total votes by panel members	Total votes for APPROVAL	% of all panel votes for APPROVAL
Antiviral Drugs	18	15	12	11	83%	61%		215	172	80%
Arthritis Drugs	9	9	8	8	100%	89%		83	81	98%
Dermatologic and Ophthalmic Drugs	8	5	2	2	63%	25%		69	40	58%
Gastrointestinal Drugs	6	4	2	2	67%	33%		62	43	69%
Pulmonary and Allergy Drugs	5	3	2	2	60%	40%		58	40	69%
Reproductive Health Drugs	4	2	1	0	50%	0%		40	20	50%
TOTAL	50	38	27	25	76%	50%		527	396	75%

Antiviral Drugs Advisory Committee Votes, 1998-2005

	1	2	3	4	5	6	7	8	9	10	11
Meeting Date	1/14/98	5/5/98	5/6/98	10/6/98	11/2/98	2/24/99	7/27/99	1/10/01	2/27/01	10/3/01	10/4/01
Product	CellCept	Priftin	Cryptaz	Epivir-HBV	Ziagen	Relenza	Rapamune	Cancidas	Valganciclovir	Viread	Vicend
Sponsor	Syntex	Hoechst Marion Roussel	Unimed	Glaxo Wellcome	Glaxo Wellcome	Glaxo Wellcome	Wyeth-Ayerst	Merck	Syntex	Gilead Sciences	Pfizer
Unanimous ?	Yes	No	No	Yes	No (7-2)	No	Yes	Yes	No	Yes	Yes
Approval? (Y-N-A)*	Yes (9-0)	Yes (10-1)	No (1-8)	Yes (6-0)	Yes (7-2)	No (4-13)	Yes (11-0)	Yes (8-0)	Yes (11-1)	Yes (12-0-2)	Yes (10-0)
TOTAL											
	Total	# Unanimous	% Unanimous								
Voting Sessions	18	12	67%								
For Approval	15	11	73%								
For Non-approval	3	1	33%								

*Votes are represented by (Yes-No-Abstain)
All votes FOR approval are counted as "yes"
All votes AGAINST approval are counted as "no"

**Abstentions are not counted

12	13	14	15	16	17	18
3/19/02	8/6/02	11/14/02	5/13/03	5/14/03	3/11/05	5/19/05
Pleconaril	Adefovir dipivoxil	Pagasays/ Capegus	Reyataz	Valtrex	Entecavir	Tipranavir
ViroPharma	Gilead Sciences	Hoffman-LaRoche	Bristol-Myers Squibb	GlaxoSmith Kline	Bristol-Myers Squibb	Boehringer Ingelheim
Yes	Yes	Yes	Yes	Yes	YES	No
No (0-15)	Yes (15-0)	Yes (12-0)	Yes (15-0)	Yes (13-0)	Yes (18-0)	Yes (10-3)
				TOTAL VOTES**	FOR Approval	%
				215	172	80%

Arthritis Drugs Advisory Committee Votes, 1998-2005

	1	2	3	4	5	6	7	8	9	
Meeting Date	08/07/98	09/16/98	12/01/98	04/20/99	07/12/00	08/16/01	03/05/03	06/25/03	09/06/05	
Product	Arava	Enbrel	Celebrex	Vioxx	Remicade	Kineret	Arava	Enbrel	Abatacept	
Sponsor	Hoechst Marion Roussell	Immunex	Searle	Merck	Centocor	Amgen	Aventis	Amgen	Bristol-Meyers Squibb	
Unanimous?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	
Approval? (Y-N-A)*	Yes (10-0) (for two indications)	Yes (17-0)	Yes (9-0)	Yes (8-0)	Yes (8-0)	Yes (6-2-1)	Yes (10-0)	Yes (6-0)	Yes (7-0)	
TOTAL										
	Total	# unanimous	% unanimous					TOTAL VOTES**	FOR Approval**	% Approval
Voting Sessions	9	8	89%					83	81	98%
For Approval	9	8	89%							
For Non-approval	0	0	0%							
*Votes here are represented by (Y-N-A) or (Yes-No-Abstain) all votes FOR approval are counted as a "yes" and all votes AGAINST approval are counted as "no"										
**Abstentions are not counted										

Dermatologic and Ophthalmic Drugs Advisory Committee Votes, 1998-2005

	1	2	3	4	5	6	7	8	
Meeting Date	07/21/99	11/04/99	05/23/02	03/17/03	09/09/03	09/10/03	07/12/04	08/27/04	
Product	Cyclosporine	Loprox	Amevive	Vitrase	Raptiva	Methyl Aminole-vulinate	Tazoral	Macugen	
Manufacturer	Allergan	Hoescht Marion Roussel	Biogen	ISTA Pharm.	Genentech	PhotoCure ASA	Allergan	Eyetech	
Unanimous?	No	No	No	No	Yes	No	No	Yes	
Approval? (Y-N-A)*	No (1-5-1)	Yes (9-3)	Yes (8-2-1)	Yes (7-5)†	Yes (11-0)	No (2-9)	No (3-8-4)	Yes (8-0)	
							TOTAL VOTES**	FOR Approval**	% Approval
TOTAL							69	40	58%
	Total	# unanimous	% unanimous						
Voting Sessions	8	2	25%						
For Approval	5	2	40%						
For Non-approval	3	0	0%						
*Votes here are represented by (Y-N-A) or (Yes-No-Abstain) all votes FOR approval are counted as a "yes" and all votes AGAINST approval are counted as "no"									
**Abstentions are not counted									
† Earlier question: Has sufficient evidence been submitted to support the efficacy of Vitrase for the treatment of vitreous hemorrhage? NO (4-8) # committee members vote to approve, although they did not believe there was evidence of efficacy (Chew, Feman, Steidl)									

Gastrointestinal Drugs Advisory Committee Votes, 1998-2005

	1	2	3	4	5	6			
Meeting Date	05/28/98	11/16/99	06/26/00	04/23/02	06/25/03	07/14/04			
Product	Avakine	Lotronex	Zelmac	Lotronex	Serostim	Zelnorm			
Sponsor	Centocor	Glaxo Wellcome	Novartis	GlaxoSmith Kline	Serono	Novartis			
Unanimous?	Yes	Yes	No	No	No	No			
Approval? (Y-N-A)*	Yes (9-0)	Yes (6-0)	No (1-6)	Yes (14-4)	No (3-6)	Yes (10-3)			
						TOTAL VOTES**	FOR Approval**	% Approval	
						62	43	69%	
TOTAL									
	Total	# Unanimous	% Unanimous						
Voting Sessions	6	2	33%						
For Approval	4	2	50%						
For Non-approval	2	0	0%						
*Votes here are represented by (Y-N-A) or (Yes-No-Abstain) all votes FOR approval are counted as a "yes" and all votes AGAINST approval are counted as "no"									
**Abstentions are not counted									

Pulmonary and Allergy Drugs Advisory Committee Votes, 1998-2005

	1	2	3	4	5	
Meeting Date	11/23/99	09/06/02	05/15/03	09/05/03	06/06/05	
Product	Advair Diskus	Spiriva	Xolair	Ariflo	Pulminiq	
Sponsor	Glaxo Wellcome	Boehringer-Ingelheim	Genetech	GlaxoSmithKline	Chiron Corp	
Unanimous?	Yes	No	Yes	No	No	
Approval? (Y-N-A)*	Yes (10-0)	Yes (8-3)	Yes (11-0)	No (3-7)	Tie vote (8-8)	
				TOTAL VOTES**	FOR Approval**	% Approval
TOTAL				58	40	69%
	Total	# Unanimous		% Unanimous		
Voting Sessions	5	2		40%		
For Approval	3	2		67%		
For Non-approval	1	0		n/a		
Tie approval vote	1	n/a		n/a		
†Voting Committee consultant June 6, 2005 meeting						
*Votes here are represented by (Y-N-A) or (Yes-No-Abstain) all votes FOR approval are counted as a "yes" and all votes AGAINST approval are counted as "no"						
**Abstentions are not counted						

Reproductive Health Drugs Advisory Committee Votes, 1998-2005

	1	2		3			
Meeting Date	04/20/98	04/10/00		12/02/04			
Product	Antocin	Uprima		Intrinsa			
Sponsor	RW Johnson	Tab Holdings		Procter & Gamble			
Unanimous?	No	No	No	Yes			
Approval? (Y-N-A)*	No (1-10-1)	Yes (10-2)	Yes (10-2)	No (0-16)			
Notes	Show of hands	(for 2 mg dose)	(for 4 mg dose)		**Votes by Individual Panel Members**		
					TOTAL VOTES**	FOR Approval**	% Approval
TOTAL					40	20	50%
	Total	# unanimous	%				
Voting Sessions	4	1	25%				
For Approval	2	0	0%				
For Non-approval	2	1	50%				
*Votes here are represented by (Y-N-A) or (Yes-No-Abstain) all votes FOR approval are counted as a "yes" and all votes AGAINST approval are counted as "no"							
**For Individual Member Votes, only roll call votes are counted and abstentions are not counted							

Devices Panels Votes Summary, 1998-2005

	Votes by Panel						Votes by Individual Panel Members		
Panel	Total panel votes on PMA's	Total Panel Votes For APPROVAL* of Device	# of Unanimous votes	Panel votes for APPROVAL* that were unanimous	% of Panel Votes for APPROVAL	% of ALL votes that were unanimous for APPROVAL	Total votes by panel members**	Total votes for APPROVAL	% of all panel votes for APPROVAL
Immunology Devices	4	3	3	3	75%	75%	29	24	83%
Microbiology Devices	3	2	2	1	67%	33%	21	12	57%
Obstetrics And Gynecology Devices	9	7	5	5	78%	56%	87	66	76%
Ophthalmic Devices	16	14	10	9	88%	56%	157	129	82%
Radiological Devices	7	6	6	6	86%	86%	45	41	91%
TOTAL	39	32	26	24	82%	62%	339	272	80%

* for approval & approval with conditions

** does not count abstentions

Immunology Devices Panel Votes, 1998-2005

	1	2	3	4			
Meeting Date	2/2/98	9/4/98	11/9/98	7/15/05			
Product	Free PSA Assay	HercepTest	FISH HER-2/neu gene	AlzheimAlert NTP Test			
Manufacturer	Hybritech	DAKO	Vysis	Nymox			
Motion	A + C	A + C	A + C	Not approvable			
Unanimous	Yes	Yes	Yes	No			
Approved? (Y – N – A)*	Yes (7-0)	Yes (6-0)	Yes (9-0)	No (2-5)	TOTAL VOTES**	FOR Approval	% Approval
TOTAL					29	24	83%
	Total	#Unanimous	%Unanimous				
Voting Sessions	4	3	75%				
For Approval	0	0	--				
For Non-Approval	1	0	--				
For Approval + Conditions	3	3	100%				
†When a motion is for non-approval, votes FOR the motion are considered votes AGAINST approval, and votes AGAINST the motion are considered FOR approval							
*Votes here are represented by (Y-N-A) or (Yes-No-Abstain) all votes FOR approval are counted as a "yes" and all votes AGAINST approval are counted as "no." When there are no abstentions, votes are counted (Y-N).							
**Abstentions are not counted							
A + C refers to Approval with Conditions							

Microbiology Devices Panel Votes, 1998-2005

	1	2	3			
Meeting Date	10/12/01	11/11/01	3/8/02			
Product	QuantiFERON-TB	Endotoxin Activity Assay	Supplement to HPV			
Manufacturer	Cellestis Limited	Sepsis, Inc.	Digene Corp.			
Motion ‡	A + C	Not Approvable	A + C			
Unanimous?	Yes	Yes	No			
Approved? (Y-N-A)*	Yes (6-0)	No (0-7)	Yes (6-2)	TOTAL VOTES**	FOR Approval	% Approval
TOTAL				**21**	**12**	**57%**
	Total	# unanimous	% unanimous			
Voting Sessions	3	2	67%			
For Approval	0	0	--			
For Non-approval	1	1	100%			
For Approval + Conditions	2	1	50%			

†When a motion is for non-approval, votes FOR the motion are considered votes AGAINST approval, and votes AGAINST the motion are considered FOR approval

*Votes here are represented by (Y-N-A) or (Yes-No-Abstain) all votes FOR approval are counted as a "yes" and all votes AGAINST approval are counted as "no". When there are no abstentions, votes are counted (Y-N)

**Abstentions are not counted

‡A + C refers to Approval with Conditions

Obstetrics and Gynecological Devices Panel Votes, 1998-2005

	1	2	3	4	5	6	7	8	9	
Meeting Date	10/20/98	1/24/00	1/29/01	4/22/02	7/22/02	6/10/03	6/3/04	5/17/05	6/23/05	
Product	Vesta Dub Treatment System	Nellcor N-400	First Option Uterine Cryoblation Therapy System	STANs21 Fetal Heart Monitor	Essure Micro-Insert Device	Microwave Endometrial Ablation System	ExAblate 2000	LUMA Cervical Imaging System	STANs31 Fetal Heart Monitor	
Manufacturer	Valley Lab, Inc	Nellcor Perinatal	CryoGen	Neoventa	Conceptus, Inc	Microsulsis	InSightec	MediSpectra	Neoventa	
Motion†	A+C	A+C	A+C	NA	A+C	A+C	A+C	NA	A+C	
Unanimous	Yes	No	Yes	No	Yes	Yes	No	No	Yes	
Approved? (Y-N-A)*	Yes (6-0)	Yes (10-1)	Yes (9-0)	No (5-6)	Yes** (8-0-1)	Yes (9-0)	Yes (8-5)	No (2-9)	Yes (9-0)	
TOTAL								TOTAL VOTES**	For Approval**	% Approval
								87	66	76%
	Total	# Unanimous	% Unanimous							
Voting Sessions	9	5	56%							
For Approval	0	0								
For Non-approval	2	0	0%							
For Approval + Conditions	7	5	71%							
†When a motion is for non-approval, votes FOR the motion are considered votes AGAINST approval, and votes AGAINST the motion are considered FOR approval										
*Votes here are represented by (Y-N-A) or (Yes-No-Abstain) all votes FOR approval are counted as a "yes" and all votes AGAINST approval are counted as "no". When there are no abstentions, votes are counted (Y-N)										
**Abstentions are not counted										
A + C refers to Approval with Conditions										

Ophthalmic Devices Panel Votes, 1998-2005

	1	2	3	4	5	6	7	8	9	10
Meeting Date	2/13/98	2/13/98	7/22/99	7/22/99	7/23/99	7/23/99	7/20/01	11/30/01	1/17/02	1/18/02
Product	PMA Scanning laser	Lasik	Thermal keratoplasty	Lasik	IOL	Lasik	Soft Contacts	Keratoplasty	Capsular Tension Ring	CRT Submission
Manufacturer	Autonomous Technologies	Kremer Excimer Laser	Sunrise Technologies	CRS Clinical	Bausch & Lomb	Summit Tech	Ciba Vision	Refractic	Morcher	Paragon Vision
Motion	A+C	NA	NA	A+C	A+C	A+C	A+C	A+C	A+C	A+C
Unanimous (Y-N-A)*	Yes	No	Yes	Yes	Yes	Yes	Yes	N	No	Yes
Approved?	Yes (6-0)	No (2-4)	No (0-12)	Yes (9-0-2)	Yes (12-0)	Yes (9-0-1)	Yes (10-0)	Yes (9-1)	Yes (8-1-1)	Yes (11-0)
Total										
	Total votes	# Unanimous		% Unanimous						
Voting Sessions	16	10		63%						
For Approval	0	0		0%						
For Non-approval	2	1		50%						
For Approval + Conditions	14	9		64%						

11	12	13	14	15	16
1/18/02	8/1/02	5/23/03	10/3/03	2/5/04	2/6/04
Quadra Lens	Custom-Cornea Myopic L.	CrystaLens	Implantable Contact Lens	ARTISAN Myopia Lens	Supplement 5 for CK System
Paragon Vision	Alcon's Refractive	C&C Vision	STAAR Surgical	OPHTEC USA	Refractec
A+C	A+C	A+C	A+C	A+C	A+C
No	Yes	Yes	No	No	Yes
Yes (10-1)	Yes (9-0)	Yes (7-0)	Yes (8-3)	Yes (7-6)**	Yes (12-0)
			TOTAL VOTES**	FOR Approval**	% Approval
			157	129	82%

†When a motion is for non-approval, votes FOR the motion are considered votes AGAINST approval, and votes AGAINST the motion are considered FOR approval

*Votes here are represented by (Y-N-A) or (Yes-No-Abstain) all votes FOR approval are counted as a "yes" and all votes AGAINST approval are counted as "no". When there are no abstentions, votes are counted (Y-N)

**Abstentions are not counted

A + C refers to Approval with Conditions

Radiological Devices Panel Votes, 1998-2005

	1	2	3	4	5	6	7			
Meeting Date	5/11/1998	8/18/1998	8/18/1998	11/6/2000	3/5/2001	12/2/2002	2/3/2004			
Product	ImageChecker For Mammograms	Caries Detector	trans-spectral impedance scanner	SIR-Spheres	Chest Radiographs	Breast thermal imagery	Image Checker For Lung Nodules			
Manufacturer	R2 Tech. Inc.	Logicon RDA	TransScan	Sirtex Medical, Ltd	Deus Tech.	Computerized Thermal Imaging	R2 Tech. Inc.			
Motion	A+C	A	A+C	A+C	A+C	NA	A+C			
Unanimous?	Yes	Yes	Yes	Yes	Yes	No	Yes			
Approved? (Y-N-A)*	Yes (6-0)	Yes (8-0)	Yes (6-0)	Yes (6-0)	Yes (5-0)	No (3-4)	Yes (7-0-1)	TOTAL VOTES**	FOR Approval	% Approval
TOTAL								45	41	91%
	Total	# unanimous		% unanimous						
Voting Sessions	7	6		86%						
For Approval	1	1		100%						
For Non-approval	1	0		0%						
For Approval + Conditions	5	5		100%						

†When a motion is for nonapproval, votes FOR the motion are considered votes AGAINST approval, and votes AGAINST the motion are considered FOR approval

*Votes here are represented by (Y-N-A) or (Yes-No-Abstain) all votes FOR approval are counted as a "yes" and all votes AGAINST approval are counted as "no". When there are no abstentions, votes are counted (Y-N)

**Abstentions are not counted

A + C refers to Approval with Conditions.

General and Plastic Surgery Advisory Panel

Of all the FDA advisory panels, the General and Plastic Surgery panel has been one of the most active and certainly the most controversial. From 1998 through 2005, the panel considered 17 applications for approval, but the six applications for breast implants received more attention than all the other medical device advisory panel meetings combined.

The General and Plastic Surgery Advisory Panel was not randomly selected to be part of the study that is the basis of this report. In light of the controversy about the panel's implant decisions, however, a separate analysis was conducted to see how the panel's voting patterns and panel members' comments compared to those of the randomly selected advisory panels in the study.

The voting patterns for the General and Plastic Surgery Advisory Panel show less consensus than most of the device advisory panels in the study. Only 41% of the 17 voting sessions were unanimous, and only 46% of the panel's approval recommendations were unanimous. In contrast, most of the device panels in the study were unanimous every time they voted for approval. Nevertheless, the percentage of votes recommending approval on the General and Plastic Surgery Advisory Panel are typical for the device advisory panels. Of the 17 general and plastic surgery medical devices reviewed by the panel, 14 (82%) were recommended for approval, almost always with conditions. Of the total of 144 General and Plastic Surgery Advisory Panel votes cast over the eight years of the study, 115 (80%) were for approval. Both those statistics are exactly identical to the average of the five device panels that were randomly selected and analyzed in the study.

It is notable that of the three products that the panel recommended against approving between 1998 and 2005, two were breast implants.

The breast implant advisory panel meetings, held in 2000, 2003, and 2005, attracted enormous media attention, featuring public comments by plastic surgeons and patients praising the implants, other patients describing debilitating pain and physical deformity from leaking implants, and numerous scientists and physicians testifying for and against approval. The panel meetings differed from most other device panel meetings in a fundamental way: although the companies involved were asking that their product be approved by the FDA for the first time, the companies had been selling the implants in the United States for many years.[a] As a result, there were many women who had implants for decades who testified about the risks and benefits of the devices.

For those attending the meetings, panel members' comments and votes seemed strangely contradictory. For example, in their review of silicone breast implants in 2003, panel members consistently and strongly criticized the lack of long-term safety data, the lack of information about the causes and consequences of implant rupture, and the "lack of obligation that the sponsor felt to pursue a better product," after which the panel recommended the implants for approval.[b]

At the 2-day meeting on saline breast implants in 2000, saline implants made by McGhan (now Inamed) and Mentor were recommended for approval with numerous conditions, despite strongly worded criticisms about the very high complication rates and the lack of long-term safety data. Saline implants made by another company, PIP, were rejected unanimously because the panel members concluded that the research studies were inferior to those of the other two companies.

At the 2-day meeting for Inamed silicone gel breast implants in 2003, the criticisms of the lack of long-term safety data were nearly unanimous and the implants seemed destined for rejection when the company saved the day by proposing a compromise with numerous unusually stringent conditions of approval. The vote was closer than is typical for FDA advisory committees, 9-6, with most approval votes coming from plastic surgeons and other surgeons, at least one of whom received a waiver from the FDA to allow him to participate despite having received a grant from Inamed.

In 2005, the FDA held a 3-day meeting to review Inamed and Mentor silicone gel breast implants. This was the first time the advisory panel recommended against approval for Inamed breast implants, voting 5-4 that the implants were non-approvable because of the high rupture rate and the failure to collect more than 3 years of longitudinal data. The next day, however, the same panel recommended approval for Mentor silicone gel breast implants, 7-2, although the company had provided only 2 years of longitudinal data on implant rupture and leakage, compared to Inamed's 3 years of rupture data.

The approval of Mentor after the disapproval for Inamed received considerable media attention, and there was speculation about the apparent contradiction between criticizing Inamed for their 3-year rupture study and being satisfied with a 2-year rupture study from Mentor. Although there were other differences in the data provided by the two companies, the basic contradiction remained. In the context of the study findings presented in this report, however, the disconnect between the panel members' explicit concerns and the unanimous and lopsided votes in favor of approval are not surprising. In fact, the pattern is very similar to other device panel deliberations. Moreover, a review of the 1998-2005 votes of the 11 advisory committees in the study in addition to the General and Plastic Surgery panel, indicates that *none of these drug or device advisory committees ever voted against approval for two products in a row in the same year, let alone the same week.* To reject two products two days in a row would have been completely inconsistent with the approval-oriented voting patterns repeatedly demonstrated in the study. This helps explain the 2005 vote in favor of Mentor implants the day after rejecting Inamed's application for a very similar product with similar research studies.

In light of the overwhelming trend toward approval among FDA medical device advisory panels and the reluctance to reject more than one product per year, the large number of panel members who expressed strong concerns and then voted for approval can be seen as typical rather than unusual. In fact, the breast implant applications received more votes against approval than the vast majority of medical devices reviewed by all six device advisory panels we studied.

[a] The FDA did not have the authority to regulate breast implants until 1976. Since breast implants were sold since the early 1960's, they were "grandfathered" and could still be sold after 1976. PMAs were first required for silicone gel breast implants in 1991, but although the implants did not obtain FDA approval, they were allowed to be sold under restricted conditions after that. Saline breast implants went through the PMA process in 1999-2000.

[b] This quote is from bioethicist Nancy Dubler, October 14, 2003 FDA meeting transcript, page 495; however, similar quotes regarding the lack of safety data are available in the FDA meeting transcripts for the implant advisory meetings in 2000, 2003, and 2005.

June 27, 2007

Caroline Loew, Ph.D.
Senior Vice President
Science and Regulatory Affairs
PhRMA
950 F Street, N.W.
Washington, D.C. 20004

Dear Dr. Loew:

Thank you for appearing before the Subcommittee on Health on Tuesday, June 12, 2007, at the hearing entitled "Legislative Hearing on Discussion Drafts Concerning Prescription Drug User Fee Act Reauthorization, Medical Device User Fee and Modernization Act Reauthorization, Drug Safety, and Certain Pediatric Pharmaceutical and Device Legislation." We appreciate the time and effort you gave as a witness before the Subcommittee.

Under the Rules of the Committee on Energy and Commerce, the hearing record remains open to permit Members to submit additional questions to the witnesses. Attached are questions directed to you from certain Members of the Committee. In preparing your answers to these questions, please address your response to the Members who have submitted the questions and include the text of the Member's question along with your response.

To facilitate the printing of the hearing record, your responses to these questions should be received no later than the close of business **Wednesday, July 11, 2007**. Your written responses should be delivered to **316 Ford House Office Building** and faxed to **202-225-5288** to the attention of Melissa Sidman, Legislative Clerk/Public Health. An electronic version of your response should also be sent by e-mail to Ms. Melissa Sidman at **melissa.sidman@mail.house.gov** in a single Word formatted document.

Thank you for your prompt attention to this request. If you need additional information or have other questions, please contact Melissa Sidman at (202) 226-2424.

Sincerely,

JOHN D. DINGELL
CHAIRMAN

Attachment

cc: The Honorable Joe Barton, Ranking Member
Committee on Energy and Commerce

The Honorable Frank Pallone, Jr., Chairman
Subcommittee on Health

The Honorable Nathan Deal, Ranking Member
Subcommittee on Health

The Honorable Jim Matheson, Member
Subcommittee on Health

PhRMA Response to Written Questions from Representative Matheson in Relation to the Subcommittee on Health, Committee on Energy and Commerce, United States House of Representatives Hearing Entitled "Legislative Hearing on Discussion Drafts Concerning Prescription Drug User Fee Reauthorization, Medical Device User Fee and Modernization Act Reauthorization, Drug Safety, and Certain Pediatric Pharmaceutical and Device Legislation" held on June 12, 2007

Response submitted by Caroline J Loew, PhD, Senior Vice President, Scientific and Regulatory Affairs, Pharmaceutical Research and Manufacturers of America (PhRMA) on July 11, 2007.

Incentives for Antibiotic Innovation

Infectious diseases have killed and crippled throughout history. Until the 1920's, infectious diseases were the leading cause of death in the United States. Vaccines, and later, antibiotics held many of these diseases at bay, but they still pose a very serious threat. Several infectious pathogens have become resistant to current treatments, and diseases once considered conquered, such as tuberculosis, have reemerged.

According to PhRMA's most recent survey of new medicines in development for infectious diseases, there are 185 medicines in testing to battle infectious disease, including 34 antibiotics. All of the medicines in development are either in human clinical trials or awaiting Food and Drug Administration (FDA) approval.

Clearly, medical need exists for new antibiotics to treat patients with resistant pathogens of public health importance. However, due to a variety of reasons, including the cost to research and develop antibiotics and the limited market if approved, new antibiotics are at a disadvantage in research and development portfolios. Additional incentives are one way to help stimulate investment in antibiotics for drug-resistant pathogens. Additional incentives that have been discussed through the years include extended market exclusivity a new antibiotic or for another prescription medicine developed by the sponsor, as well as FDA guidance on development and labeling of antibacterial drugs for treatment of resistant pathogens. While PhRMA has not taken a position on any specific incentive structure, we would be more than happy to work with the Committee on this important issue.

Orphan Drug Incentives for Antibiotics

The Orphan Drug Act of 1983 provided tax relief and some marketing exclusivity for companies that develop an orphan drug. The legislation is credited with the explosion

in drug approvals for rare diseases – defined as a condition affecting fewer than 200,000 patients in the United States – after 1983. Since 1995, more than 160 medicines were approved to treat rare diseases, compared to 108 in the previous decade, and fewer than 10 in the 1970s.

Given the definition of a rare disease, there are certainly some antibiotics that would be eligible for orphan drug designation. For example, an antibiotic to treat methicillin resistant Staph, which is often found in hospitals, would be eligible for orphan drug designation and therefore eligible for the additional incentives the Orphan Drug Act provides. Despite the existence of the incentives contained in the Orphan Drug Act, the medical need for new antibiotics remains. Therefore, it is possible that additional or alternative incentives may be needed to spur further research and development in this area.

June 27, 2007

Randall L. Lutter, Ph.D.
Associate Commissioner for Policy and Planning
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Lutter:

Thank you for appearing before the Subcommittee on Health on Tuesday, June 12, 2007, at the hearing entitled "Legislative Hearing on Discussion Drafts Concerning Prescription Drug User Fee Act Reauthorization, Medical Device User Fee and Modernization Act Reauthorization, Drug Safety, and Certain Pediatric Pharmaceutical and Device Legislation." We appreciate the time and effort you gave as a witness before the Subcommittee.

Under the Rules of the Committee on Energy and Commerce, the hearing record remains open to permit Members to submit additional questions to the witnesses. Attached are questions directed to you from certain Members of the Committee. In preparing your answers to these questions, please address your response to the Members who have submitted the questions and include the text of the Member's question along with your response.

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Sincerely,

JOHN D. DINGELL
CHAIRMAN

Attachment

cc: The Honorable Joe Barton, Ranking Member
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Subcommittee on Health

The Honorable Jim Matheson, Member
Subcommittee on Health

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

SEP 25 2007

The Honorable John D. Dingell
Chairman
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

Dear Mr. Chairman:

Thank you for providing the Food and Drug Administration (FDA or the Agency) the opportunity to testify at the June 12, 2007, hearing entitled, "Legislative Hearing on Discussion Drafts Concerning Prescription Drug User Fee Act Reauthorization, Medical Device User Fee and Modernization Act Reauthorization, Drug Safety, and Certain Pediatric Pharmaceutical and Device Legislation," before the Subcommittee on Health, Committee on Energy and Commerce. Dr. Randall Lutter, Ph.D., FDA's Deputy Commissioner for Policy, testified on behalf of FDA. We are responding to the letter of June 27, 2007, you sent in follow-up to that hearing with questions from Representative Jim Matheson. Below we have restated his questions in bold, followed by our response.

The Honorable Jim Matheson

1. **Dr. Lutter, I am concerned about antimicrobial resistance. Recent reports of the traveler with extensively drug-resistant tuberculosis or XDR-TB, have only heightened the sense that we, as a Nation, are not doing enough to fight the rise of resistant microorganisms. What is FDA doing to fight antimicrobial resistance, and how can FDA better preserve the safety of antibiotics?**

   FDA is concerned with antimicrobial resistance and its public health consequences. The Agency has been engaged in a number of activities over the years related to the issue of antimicrobial resistance. These activities include the following:

   - The Agency has participated in the drafting and implementation of the HHS Public Health Action Plan for Combating Antimicrobial Resistance.[1] Published in 2001, this broad reaching strategy demonstrates a coordinated focus on several areas including: education, product development, research and surveillance.

[1] To view the Action Plan please see http://www.cdc.gov/drugresistance/actionplan/index.htm

- FDA, the Centers for Disease Control and Prevention (CDC), and the National Institutes of Health (NIH) are planning a public meeting December 12-13, 2007, in Atlanta to present the agencies' accomplishments in the Public Health Action Plan and to ask invited consultants for their input to update the plan. Minimizing the emergence of antimicrobial resistant bacteria in animals and the potential spread to humans via the food supply is a complex problem requiring a coordinated, multifaceted approach, which involves FDA as well as other Federal agencies.

- In February 2004, FDA promulgated new regulations to mandate that the labeling for all systemic antibacterial drugs for human use contain several statements to caution healthcare providers against the inappropriate use of antibiotics.[2]

- FDA has developed a strategy for managing the potential risks associated with the use of antimicrobial drugs in food-producing animals and has held several public meetings. This innovative approach includes, for example, the use of risk assessment, robust monitoring, and research.

- FDA's Center for Veterinary Medicine (CVM) also has developed guidance for industry entitled, "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern" (Guidance #152).[3] This guidance describes a recommended risk assessment approach for assessing the safety of antimicrobial new animal drugs with regard to their microbiological effects on bacteria of human health concern. The guidance also describes possible risk management steps and provides one possible process for evaluating potential microbiological effects of such drugs as part of the new animal drug application process. As stated in Guidance #152, it contains non-binding recommendations.

- FDA withdrew the approvals of two new animal drug applications (NADAs) for the use of sarafloxacin antimicrobial drugs for the treatment of poultry on April 30, 2001 (66 *Federal Register* 21400). FDA informed the drug sponsor of a question regarding human food safety, due to the use of fluoroquinolones such as sarafloxacin in poultry, and the drug sponsor requested voluntary withdrawal of the NADAs. On July 28, 2005, FDA announced the Agency's final decision to withdraw the approval of the NADA for the fluoroquinolone antimicrobial drug enrofloxacin for the purpose of treating bacterial infections in poultry. The final rule withdrawing approval of the fluoroquinolone

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[2] See 21 CFR §201.24 Labeling for systemic antibacterial drug products. available at http://a257.g.akamaitech.net/7/257/2422/26mar20071500/edocket.access.gpo.gov/cfr_2007/aprqtr/pdf/21cfr201.24.pdf

[3] Guidance 152 available at http://www.fda.gov/cvm/Documents/fguide152.pdf

antimicrobial drug enrofloxacin was effective on September 12, 2005 (70 FR 44048, August 1, 2005).

- CVM helped establish the National Antimicrobial Resistance Monitoring System (NARMS) program to monitor changes in susceptibility of select bacteria to antimicrobial agents of human and veterinary importance. NARMS is a multi-faceted monitoring system that takes advantage of the expertise and resources of a number of Federal agencies and state public health laboratories. NARMS monitors susceptibility/resistance phenotypes using three testing sites including FDA/CVM (retail meat and poultry), CDC (humans), and USDA (animal/slaughter). The NARMS program is yielding information that is valuable in identifying the source and magnitude of antimicrobial resistance in the food supply and is important for the development of public health recommendations for the use of antimicrobial drugs in humans and food animals.

- CVM has supported the American Veterinary Medical Association (AVMA) in developing and disseminating prudent use principles for veterinarians. CDC has undertaken extensive activities to promote prudent use principles for physicians.

- FDA has clarified regulatory requirements to both industry and the scientific community. FDA makes presentations on regulatory requirements for tests of use in antimicrobial resistance initiatives several times per year to the Professional In-Vitro Diagnostics Roundtable (a group representing all major professional laboratory groups). On several occasions these discussions have specifically highlighted issues related to development of diagnostics for antimicrobial susceptibility testing. To further discussion on obstacles and issues that might exist in technology transfer, FDA's Center for Devices and Radiological Health offered protocol advice and provided an expedited review option to device manufacturers to assist them in getting an alternative method for detecting vancomycin resistance in S. aureus to market.

- FDA published a guidance document on April 10, 2006, to ensure the safe and effective use of in vitro diagnostics for detecting novel influenza A (or A/B) viruses from human specimens such as H5N1, H9N2, and H7N7. The guidance also included recommendations and information for assessing the clinical performance of these devices.

- In February 2006, FDA cleared a new assay submitted by CDC for the detection of human infection with H5 Avian Flu virus. Other recent approvals include: 10/18/06 MASTALEX-MRSA a rapid test for confirming Methicillin Resistant Staph aureus (10/18/06); Smart GBS Dx System rapid DNA test for detecting Group B strep in pregnant women (12/12/06); and ImmunoCard

STAT EHEC a rapid test for detecting Shiga toxins 1 and 2 produced by E.coli in stool specimens to aid in the diagnosis of diseases caused by enterohemorrhagic E.coli (EHEC) infections (2/14/07).

- FDA is reviewing applications for novel therapeutic approaches using immunoglobulin for prevention of serious lower respiratory tract diseases caused by respiratory synctial virus and sepsis. Also, FDA is studying the spread of antibiotic resistance, the mechanisms of resistance, and development of strategies to recover use of existing antibiotics as part of its biodefense programs. FDA recently awarded a contract to Microbiotix, Inc., for the study of novel antibiotics.

- CDER routinely requests studies to understand mode of action and investigate mechanism of resistance when advising pharmaceutical sponsors about antimicrobial drug development programs. (Please also see the response to question #3.)

Although FDA has been involved in numerous activities, effectively addressing the issue of antimicrobial resistance requires active participation of multiple groups beyond FDA. Other government organizations, academia, industry, professional societies, healthcare practitioners, and the public are among the groups that also play a role in responding to antimicrobial resistance.

2) **When FDA approves an antimicrobial drug, how does the agency ensure that the drug will not be inappropriately used and end up contributing to antimicrobial resistance?**

FDA's Center for Drug Evaluation and Research (CDER) is currently working on developing draft guidance to industry on the development of antibacterial drugs for several indications. These guidances will provide advice to sponsors about clinical trial designs intended to better detect a new product's benefit. Having better information relating to a product's benefits will allow one to better weigh the benefits against the risks of an antimicrobial drug which should help to provide information to foster appropriate antimicrobial use. Healthcare providers and their patients will be able to make more informed prescribing decisions with the availability of better evaluation of the benefit/risk ratio.

The Agency is limited in its authority to influence typical "inappropriate use" because prescribing by healthcare practitioners falls within the practice of medicine; the Agency does not regulate the practice of medicine. However, product labeling describes the drug's approved indications, adverse effects and other safety information, microbiology information including susceptibility test interpretive criteria ("breakpoints"), and information on modes of action and mechanism of resistance,

when available. All systemic antibacterial drugs for human use also need to contain statements about appropriate use in the product label. The information in the product label determines how the drug can be legally marketed. However, as noted previously, we have limited authority to address the issue of typical "inappropriate use" which may occur at the level of the prescriber and patient.

3) **What formal consideration is given in FDA's review of antimicrobial drug applications to issues of antimicrobial resistance?**

With the knowledge that resistance to new antimicrobials is an important public health matter, FDA typically asks for studies to help define the potential for the development of resistance to new antimicrobials during the period of time the drug is under development. These studies characterize the method(s) by which the antimicrobial inhibits the growth of or kills the bacteria (mode of action) as well as the potential mechanisms by which the bacteria may become resistant to the antimicrobial. An understanding of the mode(s) of action provides information as to what mechanism(s) of antimicrobial resistance have the potential to develop as well as how quickly resistance might develop once the drug becomes available for use. If the mode of action of the drug is similar to the mode of action of other existing antimicrobials, resistance may occur sooner because there are multiple drugs that provide the same or similar selective pressure leading to resistance. Sponsors also perform studies to determine if resistance to the new antimicrobial results in resistance (cross-resistance) to other antimicrobials.

In addition to laboratory studies to determine the mode(s) of action and development of resistance, new antimicrobials are also tested in animals and patients and consider how dose selection will affect eradication of the infecting organism and also potential effects on the development of resistance. Data that contribute to these determinations are complex and require considerable testing during the product's development. The findings from the laboratory and clinical studies that are done to characterize the parameters of an antimicrobial as they relate to mode(s) of action, potential mechanism(s) of resistance, pharmacokinetic studies and interpretation of laboratory testing results are summarized in the product label. Attention to these details in the product label is considered essential, because the rate of development of antimicrobial resistance may be increased if the antimicrobial is dosed or used inappropriately.

With regard to antiretroviral drugs, FDA analyzes data on resistance and resistance mutations to identify which drugs can be used following others based upon information on viral resistance. Information on antiretroviral resistance and cross-resistance is included in product labeling for healthcare professionals.

4) **What is expected of the manufacturer to preserve the efficacy and safety of their antibiotic?**

The manufacturer may not promote a drug for off-label uses. In addition, the manufacturer is required to label all systemic antibacterial drug products for use in humans with language that cautions prescribers against inappropriate use. (Please see the second bulleted item in the response to question #1.) FDA regulations require the following statement on the labels of all systemic antibacterial human drug products:

> *To reduce the development of drug-resistant bacteria and maintain the effectiveness of (insert name of antibacterial drug product) and other antibacterial drugs, (insert name of antibacterial drug product) should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.*[4]

In addition, in some selected cases, manufacturers agree to monitor the development of resistance as a post-marketing commitment at the time of approval.

5) **When considering approval of an antimicrobial for a less serious illness, does FDA consider how the approval might increase microbial resistance to that drug, or other antimicrobial agents, when they are used for more serious infections?**

Excessive use of antimicrobials, which may occur in the case of treating less serious illnesses, can increase the rate at which resistance to the same antimicrobials develops. This in turn may decrease their effectiveness against treating infections, including more serious ones. How use of an antimicrobial drug "might increase microbial resistance" in the future is difficult to assess, much less weigh in to an overall assessment of risk and benefit at the time of a marketing application. We do, however, evaluate the information on resistance available from laboratory studies, animal models, and clinical trials in the application and provide that information to healthcare providers through the product label.

As mentioned in the response to question #2, the Agency is focusing on refining the standards by which antimicrobial products are evaluated in clinical trials, particularly for less serious infections. This will help to ensure that a drug will not be approved for a less serious illness without statistically robust data to support its use in that indication. Better quality clinical trial data to characterize benefits will allow one to weigh the benefits against the risks and should help to provide information that should foster appropriate usage.

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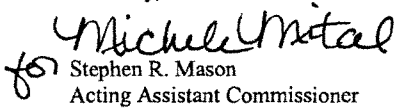
[4] http://a257.g.akamaitech.net/7/257/2422/26mar20071500/edocket.access.gpo.gov/cfr_2007/aprqtr/pdf/21cfr201.24.pdf

We believe that it would be problematic, within the scope of the FD&C Act, for FDA to restrict the use of certain antibiotics for more serious illnesses if the applicant demonstrates that the product is safe and effective against less serious illness.

Sincerely,



for Stephen R. Mason
Acting Assistant Commissioner
for Legislation

June 29, 2007

Randall L. Lutter, Ph.D.
Associate Commissioner for Policy and Planning
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Lutter:

Thank you for appearing before the Subcommittee on Health on Tuesday, June 12, 2007, at the hearing entitled "Legislative Hearing on Discussion Drafts Concerning Prescription Drug User Fee Act Reauthorization, Medical Device User Fee and Modernization Act Reauthorization, Drug Safety, and Certain Pediatric Pharmaceutical and Device Legislation." We appreciate the time and effort you gave as a witness before the Subcommittee.

Under the Rules of the Committee on Energy and Commerce, the hearing record remains open to permit Members to submit additional questions to the witnesses. Attached are questions directed to you from certain Members of the Committee. In preparing your answers to these questions, please address your response to the Members who have submitted the questions and include the text of the Member's question along with your response.

To facilitate the printing of the hearing record, your responses to these questions should be received no later than the close of business **Monday, July 16, 2007**. Your written responses should be delivered to **316 Ford House Office Building** and faxed to **202-225-5288** to the attention of Melissa Sidman, Legislative Clerk/Public Health. An electronic version of your response should also be sent by e-mail to Ms. Melissa Sidman at **melissa.sidman@mail.house.gov** in a single Word formatted document.

Thank you for your prompt attention to this request. If you need additional information or have other questions, please contact Melissa Sidman at (202) 226-2424.

Sincerely,

JOHN D. DINGELL
CHAIRMAN

Attachment

cc: The Honorable Joe Barton, Ranking Member
Committee on Energy and Commerce

The Honorable Frank Pallone, Jr., Chairman
Subcommittee on Health

The Honorable Nathan Deal, Ranking Member
Subcommittee on Health

The Honorable Marsha Blackburn, Member
Subcommittee on Health

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

The Honorable John D. Dingell
Chairman
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

JUL 23 2007

Dear Mr. Chairman:

Thank you for providing the Food and Drug Administration (FDA or the Agency) the opportunity to testify at the June 12, 2007, hearing entitled, "Legislative Hearing on Discussion Drafts Concerning Prescription Drug User Fee Act Reauthorization, Medical Device User Fee and Modernization Act Reauthorization, Drug Safety, and Certain Pediatric Pharmaceutical and Device Legislation" before the House Committee on Energy and Commerce, Subcommittee on Health. This is in response to your letter of June 29, 2007, conveying questions for the record to Dr. Randall Lutter, Deputy Commissioner for Policy, FDA's witness at the hearing. As requested, we are repeating the questions below and directing our replies to the author, Congresswoman Blackburn.

Questions from The Honorable Marsha Blackburn

1. **Some of the provision regarding restricting distribution and use strike me as potentially putting drug manufacturers in the position of being liable for the actions of physicians. They also seem to be getting Congress or the FDA into the practice of medicine. Has it not been our policy so far to avoid provisions that get into the practice of medicine? Can you comment on those provisions?**

For a small number of drugs with both unusual risks and significant benefits, restricted distribution plans are needed to assure that these drugs can be used safely. It is the plans' ability to mitigate the risks of these drugs that enables FDA to approve them. Restricted distribution plans thus increase therapeutic options available to physicians. We note that the proposed restricted distribution provisions have their complement in long-standing medical device provisions, i.e., since passage of the Medical Device Amendments of 1976, FDA has had the authority to restrict the distribution of a device if there cannot otherwise be reasonable assurance of its safety and effectiveness. Furthermore, FDA drug regulations authorize restrictions on distribution necessary to assure safe use of the drug (Title 21, Code of Federal Regulations 314.520).

FDA's objective is not to hold drug manufacturers that distribute drugs in compliance with restricted distribution plans responsible for the actions of physicians who, without the manufacturers' knowledge, deviate from the terms of those plans. Nor does FDA wish to interfere with the practice of medicine, as that policy has long been understood. FDA has a long-standing policy of not interfering with the practice of medicine, meaning that the Agency does not prevent physicians' "off-label" use of an approved drug, for instance, prescribing the drug for a condition for which it was not approved.

Accordingly, FDA generally does not take action against practitioners who fail to comply with restricted distribution plans. Manufacturers are not held responsible for deviations from such plans of which they are unaware; rather they are expected to follow the commitments they have made in association with restricted distribution plans.

2. **Some have claimed that the 3rd party inspection program has not been utilized and that companies have decided it is not in their interest to do so. There have also been claims that the proposed modifications to the program would not impact the utilization of 3rd party inspectors. Do you agree with that assessment? And do you feel that there are companies that want to use 3rd party inspection programs if modifications to the program were made?**

Both FDA and the medical device industry would benefit from the reauthorization of the third party accredited person (AP) inspection program, with some modifications. In a report issued this year, the Government Accountability Office found that potential incentives for industry participation in the program include the opportunity to reduce the number of inspections conducted to meet FDA and other countries' requirements and the ability to control the scheduling of these inspections.[1] With wider industry participation, FDA could receive more information about the medical devices marketed in the United States and could focus its inspectional resources on those products and companies posing the greatest risk to public health.

There has been little industry participation in the program to date. During FDA's meetings with industry to discuss reauthorization, industry representatives stated that one reason for their lack of participation was the administrative burdens associated with the petition and approval process. Industry representatives indicated that companies would be more likely to participate if some of those burdens were removed. As a result, FDA and industry agreed to recommend that Congress reauthorize the program, but replace the petition process with a process that required notice of intent to use an AP, while maintaining the conflict-of-interest prohibitions and FDA's authority to refuse a company's participation or the selection of a particular AP, which Congress granted under the original program.

3. **Wouldn't the 3rd party inspection programs allow FDA to focus its resources on those areas of higher risk while still allowing the Agency to receive more information from inspections from lower risk facilities?**

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1. Medical Devices: Status of FDA's Program for Inspections by Accredited Organizations, GAO-07-157, January 5, 2007.

Yes. One of the requirements to participate in the program is that a company's prior inspection result must be either "no action indicated" or "voluntary action indicated." These are establishments whose last inspection indicated that they were in compliance with, or had only minor deviations from, FDA's quality systems requirements. FDA would have less concern about the public health risk posed by these establishments than by establishments whose prior inspection result was "official action indicated." With wider industry participation, APs would be covering a greater number of lower risk establishments and FDA could focus even more of its inspectional resources on higher risk establishments, those with established compliance problems and those with no inspectional history at all.

Thank you again for the opportunity to participate in this important hearing. If you have any further questions, please contact us.

Sincerely,

Stephen R. Mason
Acting Assistant Commissioner
for Legislation

July 2, 2007

Mr. James Guest
President and CEO
Consumers Union
101 Truman Avenue
Yonkers, NY 10703

Dear Mr. Guest:

Thank you for appearing before the Subcommittee on Health on Tuesday, June 12, 2007, at the hearing entitled "Legislative Hearing on Discussion Drafts Concerning Prescription Drug User Fee Act Reauthorization, Medical Device User Fee and Modernization Act Reauthorization, Drug Safety, and Certain Pediatric Pharmaceutical and Device Legislation." We appreciate the time and effort you gave as a witness before the Subcommittee.

Under the Rules of the Committee on Energy and Commerce, the hearing record remains open to permit Members to submit additional questions to the witnesses. Attached are questions directed to you from certain Members of the Committee. In preparing your answers to these questions, please address your response to the Members who have submitted the questions and include the text of the Member's question along with your response.

To facilitate the printing of the hearing record, your responses to these questions should be received no later than the close of business **Wednesday, July 11, 2007**. Your written responses should be delivered to **316 Ford House Office Building** and faxed to **202-225-5288** to the attention of Melissa Sidman, Legislative Clerk/Public Health. An electronic version of your response should also be sent by e-mail to Ms. Melissa Sidman at **melissa.sidman@mail.house.gov** in a single Word formatted document.

Thank you for your prompt attention to this request. If you need additional information or have other questions, please contact Melissa Sidman at (202) 226-2424.

Sincerely,

JOHN D. DINGELL
CHAIRMAN

Attachment

cc: The Honorable Joe Barton, Ranking Member
Committee on Energy and Commerce

The Honorable Frank Pallone, Jr., Chairman
Subcommittee on Health

The Honorable Nathan Deal, Ranking Member
Subcommittee on Health

The Honorable Jim Matheson, Member
Subcommittee on Health

Disclosure of clinical trials

The registration and public disclosure of clinical trials and other studies is key to determining the safety of drugs. Transparency of study results is necessary to understand the true safety and efficacy of drugs, to identify further research efforts and to ensure appropriate safety warnings. Too often, pharmaceutical companies distort, manipulate and conceal results from clinical studies in order to guarantee the approval of their drug. Today, there is an enormous bias toward reporting favorable results and hiding or minimizing of lackluster and negative results. As one analyst has written:

> "Another problem with the existing system is that non-publication of negative trials and non-reporting of negative outcomes, coupled with redundant publication of positive findings, has led to systematic publication bias, which can undermine the reliability of medical evidence."[12]

Two such examples are Vioxx and Paxil. Vioxx was removed from the market in 2004 after clinical trials revealed an increased risk of heart attack and stroke for those taking the drug.[3] According to testimony from Dr. Sandra Kweder, deputy director of the FDA's Office of New Drugs (OND), these trial results were not made available to the FDA prior to Merck's voluntary withdrawal of the drug.[4] Similarly, GlaxoSmithKline, maker of Paxil, concealed results from clinical trials linking the drug to an increased risk in suicidality among adolescents, as proven by New York Attorney General Eliot Spitzer's successful complaint against GlaxoSmithKline.[5] These trials also revealed that the drug was actually less effective than placebos among adolescents.[6] [7] Since then, the Psychopharmacologic Drugs Advisory Committee was convened on December 13, 2006, to discuss the risks of suicidality in adult populations; they recommended an extension of the black box warning to cover adult populations in their middle twenties.

There are other examples of "forgotten" studies. For example, as recently as September 29, 2006, the FDA released a Public Health Advisory that Bayer, maker of Trasylol, failed to inform the FDA Advisory Committee (which had convened eight days earlier on September 21, 2006 to discuss Trasylol) of a new observational study that revealed an increased risk of death, serious kidney damage, congestive heart failure and stroke.[8] The FDA began conducting a review of Trasylol in January, 2006, after two published research articles reported serious risks associated with use of the drug.[9] [10]

Such research misconduct has contributed to injuries and deaths by consumers who use these potentially dangerous drugs, and USA Today reports that the pharmaceutical industry faced more product liability lawsuits than any other industry last year.[11] And industry compliance with trial registration may actually be declining. Senator Grassley has reported that "industry compliance with registering clinical trials for experimental cancer treatments waned between 2004 and 2005." Apparently compliance with mandatory reporting was only 70 percent of the time in 2004 and fell to 67 percent in 2005.[12]

Abuses in the registration and reporting of clinical trial and study results highlight the need for increased transparency. Such transparency would enable the scientific community to better assess the true safety and efficacy of drugs. The World Health Organization (WHO) has taken steps to standardize trial registration and reporting through the International Clinical Trial Registry Platform (ICTRP), identifying a 20-item minimal dataset for all clinical trials, which includes target sample size and primary and secondary outcomes.[13] Many medical journals have formally supported these steps taken by the WHO and will now consider the publication of the results of a clinical trial only if it has been registered before the enrollment of the first patient.[14] The International Committee of Medical Journal Editors has just announced that they will require the registration of all Phase I trials, effective July 1, 2008.[15]The Journal of the American Medical Association is responding even more aggressively to ensure accuracy in data analysis by requiring all submissions of clinical trial results funded by industry to hire an independent statistician to analyze the data.[16] A coalition of over 100 health care stakeholders have signed the Ottawa Statement, making a moral case for full disclosure:

> "When members of the public agree to participate in trials, it is on the understanding that they are contributing to the global body of health-related knowledge. It is thus unethical to conduct human research without ensuring that valid descriptions of the study and its findings are publicly available."[17]

The need for registration of clinical trials (at all phases) became even clearer after the 2006 Phase 1 TGN1412 trial in which 6 healthy UK volunteers suffered catastrophic multi-organ failure after taking the drug. Many argue that these events could have been avoided had trial information been available for public review.[18] Although pharmaceutical companies argue that disclosing such sensitive information would allow competitors to conduct similar trials of their own, the WHO and many others in the field find that these concerns are not sufficient to delay disclosure.[19] Given the extraordinarily aggressive patenting of all aspects of a new drug, we do not believe that these public registrations will cause proprietary commercial losses. Disclosure of the TGN1412 trial would have allowed experts to determine if the trial was generally appropriate and if the procedures that were followed were sound.[20]

In addition to the lack of safety for individuals enrolled in some trials, there is the safety problem created by fraud in the falsification of data used to justify a drug's approval. In the recent case of Ketek, the FDA found multiple instances of fraud in the company's clinical trial of about 24,000 patients, some cases of which the maker Sanofi already knew about yet failed to notify the agency.[21]

Beyond the issue of outright fraud is the problem of bias in results that can distort science and endanger public health. For example, The April 1, 2007 issue of CANCER (the peer-reviewed journal of the American Cancer Society), noted that

> "Breast cancer treatment trials supported by the pharmaceutical industry are more likely to report positive results than non-sponsored studies.... In addition, there there are significant differences in the design of trials and types of questions

> addressed by pharmaceutical industry sponsored trials compared to non-sponsored trials."[22]

The Institute of Medicine report recommends that, at a minimum, all Phase 2-4 trials be registered, including a posting of a 'structured field summary of the efficacy and safety results of the studies.'[23] Furthermore, trial registration will do nothing to diminish publication bias and misreporting if only trials that have been completed and reveal favorable results are reported and published.[24] In order to really address the problem of selective reporting – which is clearly an issue given recent history – all clinical trials should be registered.

In addition, some argue that even Phase 1 trials can gather data on efficacy in addition to safety, and therefore should also be subject to registration.[25] Dr. Steven Nissen, testified before the Senate HELP Committee on November 16, 2006:

> When drugs show serious toxicity in patients, the results are rarely published. Accordingly, other companies subsequently expose patients to closely-related drugs without knowing that their competitors' study of a similar agent showed significant harm. I am aware of a class of drugs where more than a dozen compounds showed serious toxicity, resulting in termination of development, but without a single publication of results. In my view, when a patient volunteers to participate in a drug or device study, there is an implicit moral obligation that the patient's participation will benefit medical science. When studies are not published, we learn nothing from the experiment and make the same mistakes over and over again.

The data found in a Phase 1 trial can contribute to meta-analyses of adverse events and is used by successful safety projects such as RADAR.[26] Finally, as Dr. Nissen implied, there is a strong moral argument for such registration: fellow human beings have volunteered to serve basically as guinea pigs to test the basics of a new drug idea. If there is any adverse side effect from such tests, it seems immoral not to report such results and not to warn other companies who may stumble down the same research pathway. There may be little merit in the concern that a company will lose 'proprietary' data. There is already precedent in the 2002 Best Pharmaceuticals for Children Act (BPCA) of the publication of unsuccessful results.[27] A company's proprietary and commercial interests are undoubtedly protected by the aggressive patenting that occurs in the drug industry. The safety of human test subjects should come first.

Congress should also consider whether observational trials that meet certain quality standards should begin to be included in a central registry. While Randomized Clinical Trials are clearly the scientific gold standard, the recent observational review of Aprotinin (Trayslol) and its impact on heart operation patients over a five year period (and the fact that the manufacturer 'neglected' to provide one such study to a FDA Advisory Committee in the fall of 2006) is an example of the kind of sophisticated study that should be part of the public record. As a recent editorial in JAMA concluded:

"The concept that observational data sets and analyses can play a substantial role in postmarket surveillance and safety evaluation for drugs and devices has enormous merit and, many believe, feasibility."[28]

1

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[3] Curfman, et al. Expression of Concern: Bombardier et al., "Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis," N Engl J Med. 2000;343:1520-8. New England Journal of Medicine. 2005; 353: 2813-2814.

[4] U.S. Congress. Senate. Committee on Finance. Hearing on "FDA, Merck and Vioxx: Putting Patient Safety First?" Testimony of Sandra Kweder, M.D. (November 18, 2004).

[5] People of the State of New York v. GlaxoSmithKline and SmithKline Beecham Corporation.

[6] Ibid.

[7] Another example involves Celebrex, and the withholding of data showing it was no more effective than other drugs in reducing ulcers. See article in Law and Contemporary Problems: Access to Pharmaceutical Data at the FDA (Public Citizen Health Research Group Publication #1789, by Lurie and Zieve).

[8] FDA Public Health Advisory: Aprotinin Injection (marketed as Trasylol). (September 29, 2006).

[9] FDA Public Health Advisory: Aprotinin Injection (marketed as Trasylol). (February 8, 2006).

[10] Mangano DT, Tudor IC, and Dietzel C. The risk associated with aprotinin in cardiac surgery. N Engl J Med. 2006; 354:353-365.

[11] Schmit, Julie. "More drugs get slapped with lawsuits." USA Today. August 23, 2006.

[12] InsideHealthPolicy, "Grassley: Slipping Compliance with Registry Shows Need for Bill," May 8, 2006.

[13] World Health Organization. World Health Organization international clinical trials registry platform: Unique ID assignment. Geneva: World Health Organization; 2005.

[14] DeAngelis CD, Drazen JM, Frizelle FA, Haug C, Hoey J, et al. Clinical trial registration: A statement from the International Committee of Medical Journal Editors. JAMA. 2004; 292: 1363–1364.

[15] JAMA, June 4, 2007.

[16] Fontanarosa PB, Flanagin A, DeAngelis CD. Reporting Conflicts of Interest, Financial Aspects of Research, and Role of Sponsors in Funded Studies. JAMA. 2005; 294: 110-111.

[17] Ottawa Statement on Trial Registration, http://ottawagroup.ohri.ca/statement.html.

[18] Kenter MJH and Cohen AF. Establishing risk of human experimentation with drugs: lessons from TGN1412. The Lancet. 2006; 368: 1387-1391.

[19] Establishing transparency to restore trust in clinical trials. The Lancet Neurology. 2006; 5: 551.

[20] Goodyear M. Learning from the TGN1412 trial. BMJ. 2006; 332: 677-678.

[21] "Designer Labeling," by Ramsey Baghdadi, The RPM Report, November, 2006. It is equally disturbing that the FDA did not disclose this known fraud to the Advisory Committee members who met to review Ketek.

[22] CANCER, press release dated February 26, 2007, "Drug Industry Increasingly Influences Breast Cancer Research."

[23] Ibid.

[24] Ibid.

[25] Rennie D. Trial registration; a great idea switches from ignored to irresistible. JAMA. 2004;292:1359-62.

[26] Bennett, C.L., et al., « The Research on Adverse Drug Events and Reports (RADAR) Project, JAMA, May 4, 2005, Vol. 293, No. 17.

[27] Testimony of Dr. Sandra Kweder, FDA, before HELP Committee, March 1, 2005: "...section 9 of BPCA gives FDA important new disclosure authority. BPCA requires that, no later than 180 days after the submission of studies conducted in response to a Written Request (for a pediatric study), the Agency must publish a summary of FDA's medical and clinical pharmacology reviews of those studies. Moreover, we must publish this information regardless of whether our action on the pediatric application is an approval, approvable, or not-approvable action....This information provides a rich source of valuable safety information to allow pediatricians to make more informed decisions about whether and how to use these drugs in their patients."

[28] "Aprotinin—Are There Lessons Learned?" editorial by Dr. T. Bruce Ferguson, JAMA, February 7, 2007 (Vol. 297, No. 5), page 528.

Response to questions from Congressman Jim Matheson from Jim Guest, President and CEO of Consumers Union

Surveillance and Data Collection/Reporting

1. *Mr. Guest, your organization has warned of the dangers of Methicillin-resistant Staphylococcus aureus (MRSA) and directed individuals to contact their Governors requesting that State health agencies survey hospitals to determine which ones are using active surveillance to prevent MRSA and to make that information public. I was impressed to see that more than 40,000 letters have been sent to States on this issue. In my own State of Utah, the number of children with MRSA infections at the Primary Children's Medical Center in Salt Lake City, has increased by almost 20 fold since 1989.*

   I understand the interest in providing better information to the public about which hospitals use successful, evidence-based techniques to prevent MRSA. Do we need to do more to address this patient safety issue? For example, should we ensure better surveillance systems that can detect safety problems more accurately and more quickly?

   First, thank you Congressman Matheson for your long interest and leadership in calling attention to the many life-and-death issues around MRSA and other infections. Your interest in developing safe use of effective antibiotics – and in ways that we can combat the growing level of MRSA and other infections in our communities and medical facilities – is commendable.

   We absolutely need more effective antibiotics to combat these dangerous infections. The best estimates are that about 10 Americans die every hour of every day from health care acquired infections (HAIs).

   The basic problem is that use of antibiotics has supplanted strong prevention practices within our hospitals and health care systems, and that has lead to more and more infections resistant to the routine use of antibiotics. We can deal with this public health crisis with very simple but effective tools. In addition to strict hand hygiene, successful strategies recommended by the Society for Healthcare Epidemiology of America (SHEA) for controlling MRSA include "active surveillance" (screening intensive care unit and other high risk patients), isolating and decolonizing MRSA carriers, using gowns, gloves, and masks when treating them to prevent its spread to other patients, and routine decontamination of patient rooms and operating rooms.

   Many hospitals, for example in northern Europe, have used these strategies to control MRSA for decades. Likewise, a number of hospitals in the U.S. that follow these infection control strategies have documented impressive results.

Unfortunately, most U.S. hospitals are not following these successful infection control practices. A June 2007 report by the Association for Professionals in Infection Control and Epidemiology (APIC) found that only less than half (45 percent) of hospitals are tracking infections throughout the hospital – the rest are focusing only on intensive care, surgical, or high risk nursery patients. Further, only 28 percent reported screening high risk patients for MRSA to identify patients who are MRSA carriers. The National Quality Forum has noted that studies have shown that hand washing compliance rates in U.S. hospitals are generally less than 50 percent.

Therefore, we hope that as the Energy & Commerce Committee considers Medicare and/or Medicaid legislation this year, that you can find a way to highlight this public health crisis, provide patients and consumers with information about the extent of the problem in their local hospitals, and adjust Medicare or Medicaid's payment policies so that our nation's health care community begins to treat this problem with the seriousness it deserves.

We strongly endorse Rep. Tim Murphy's bipartisan bill, HR 1174, and urge all Members of the House to cosponsor it. This bill provides for the public reporting of HAIs and a pilot program to help hospitals initiate anti-infection programs. The bill uses Centers for Disease Control definitions and provides for quarterly reporting of one or more health-care-associated infections selected by the Secretary.

Consumers Union is disappointed that CMS in its recent Federal Register regulation [CMS-1533-P] on hospital payment changes failed to include four major infections, including MSRA, in its list of avoidable events for which Medicare will no longer reimburse hospitals. CMS cited problems of coding and of determining where and how an individual acquired the infection as reasons not to proceed in the near future. The CMS Federal Register discussion indicated over 700,000 individuals are impacted each year by these four types of infection (MRSA, ventilator associated pneumonia, vascular catheter-associated infections, and surgical site infections). The agency also provided some data showing that the extra annual cost to the health care system from HAIs must run into the billions of dollars. Given the magnitude of the problem, we urge Congress to legislate more urgency in addressing this problem. We hope you can require within two years the implementation of coding and testing procedures that will, as you say, 'ensure better surveillance systems that can detect safety problems more accurately and more quickly.'

Consumers Union believes that by requiring public reporting, consumers (and the professionals who work at the hospitals) will ensure that actions are taken to reduce the rate of infections. We also believe that legislation can be drafted that could be scored by CBO for large savings by identifying HAIs and setting a date after which Medicare and Medicaid will not pay for the extra costs of such infections. The June MedPAC report, for example, discusses the problem of

hospital readmissions, provides some evidence of how often HAI is a cause of re-admission, and suggests some ways to identify avoidable infections which should not be reimbursed by Medicare. The MedPAC proposal, applied to Medicare, or for reasons of jurisdiction, Medicaid, could certainly help achieve dollar savings while also saving lives and improving quality.

Resistance Impact Statements and Management Plans

2. *Mr. Guest, your testimony discusses the potential benefit of Risk Evaluation and Mitigation Strategies—REMS—to enhance safety, without slowing the approval of new drugs. With your organization's interest in resistant 'super bugs' like MRSA, have you considered the importance of requiring such statements and mitigation strategies for antibiotics? Do you agree that we should ask manufacturers for their best information in this area to protect patient safety, as well as to preserve antibiotics' effectiveness for the long-term?*

   Yes. It is essential that more be done to determine which antibiotics are safest and most effective in dealing with various infections. We hope that the Conferees on HR 2900 and S. 1082 could agree to report language requiring that some of the earliest Active Surveillance research projects (section 905 of HR 2900; section 201 of S. 1082) concentrate on the study of antibiotics and when, where, and how to best use them.

   The REMS system can be particularly helpful in improving the use of antibiotics if it is used to ensure:

   - assessment of the potential for development of resistance to a new antibiotic;
   - specific strategies for minimizing misuse of a new antibiotic for indications for which it is not known to be effective; and
   - informing practitioners and FDA of current resistance patterns.

   Also, it is clear that many physicians are routinely over-utilizing antibiotics. As the Committee deals with the reform of the Medicare physician payment system and the measurement of physician quality, we hope that you could make antibiotic use (or misuse) a key pay-for-performance subject area. If physicians realize that future bonuses and quality ratings are dependant on understanding the best use of antibiotics, we can help prevent the spread of antibiotic resistant strains of bacteria, thus saving lives and money in the future.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

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June 7, 2007

The Honorable Anna Eshoo
United States House of Representatives
Washington, DC 20515

Dear Representative Eshoo:

On behalf of the 60,000 pediatricians, pediatric medical subspecialists and pediatric surgical specialists of the American Academy of Pediatrics, I would like to express our strong support for H.R. 2589, legislation to continue and strengthen the effort to ensure that prescription drugs used in children are safe and effective. The Improving Pharmaceuticals for Children Act of 2007 will reauthorize two programs that have changed pediatric practice by giving pediatricians more information needed to correctly treat their young patients.

It is an unfortunate reality today that up to two-thirds of drugs are still not labeled for use in pediatric populations. Pediatricians and families deserve complete information regarding the safety and effectiveness of the drugs they give their patients and children. Since their inception, the Pediatric Research Equity Act (PREA) and the Best Pharmaceuticals for Children Act (BPCA) have together generated more pediatric drug information in the past decade than in the previous 70 years. Your legislation not only reauthorizes these vitally important programs, but also makes many necessary improvements that will guarantee their continued success.

H.R. 2589 will increase the transparency and accountability of BPCA and PREA and will make sure that the important information they generate gets into the hands of physicians. It will improve and better integrate the successful two-pronged approach of BPCA and PREA. The bill also gives FDA the permanent authority to require pediatric studies, recognizing that children deserve safety measures that do not expire.

Thank you for your strong advocacy on behalf of children. We look forward to working with you to ensure speedy passage of this legislation.

Sincerely,

Jay E. Berkelhamer, MD, FAAP
President

JEB/mdm

ELIZABETH GLASER PEDIATRIC AIDS FOUNDATION

June 12, 2007

Honorable Anna Eshoo
U.S. House of Representatives
Washington, DC 20515

Dear Representative Eshoo:

On behalf of the Elizabeth Glaser Pediatric AIDS Foundation, I want to express our support for H.R. 2589, the *Improving Pharmaceuticals for Children Act of 2007*, which reauthorizes two important and successful laws – the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). We appreciate your long-standing commitment to ensuring that children have drugs that are safe and effective for their use and look forward to working with you toward passage of this legislation.

The *Improving Pharmaceuticals for Children Act* renews BPCA, groundbreaking legislation that created incentives to encourage pharmaceutical companies to perform studies in children. H.R. 2589 also renews PREA, a law which empowers the Food and Drug Administration to require pharmaceutical companies to test certain drugs for children. We are very pleased that this bill includes a provision to make the PREA requirement permanent. This is an important step toward ensuring that children have the same access to safe and effective medicines that we expect for ourselves as adults.

The combination of BPCA and PREA has created a carrot-and-stick mechanism that is credited with a dramatic increase in information about the safety and efficacy of children's medicines. In the decade since this mechanism was first put into place, over 180 drugs have been relabeled for children. Both laws will expire this year unless Congress acts.

We note that H.R. 2589 does not include any modification to the period of exclusivity granted for pediatric studies of blockbuster drugs. While we strongly support your legislation, we would support the addition of a provision to address the small percentage of drugs for which exclusivity has far exceeded the incentive it was intended to provide pharmaceutical companies.

Thank you again for your outstanding leadership on behalf of children. We look forward to working with you as this legislation moves forward.

Sincerely,

Pamela W. Barnes
President and Chief Executive Officer

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The New York Times

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Potentially Incompatible Goals at **F.D.A.**

BYLINE: By GARDINER HARRIS

SECTION: Section A; Column 4; National Desk; NEWS ANALYSIS; Pg. 14

LENGTH: 1435 words

Safety and speed are the yin and yang of drug regulation. Patients want immediate access to breakthrough medicines but also want to believe the drugs are safe.

These goals can be incompatible. Race a drug to market and much is likely to remain unknown when patients take it. Test a drug thoroughly to assess all possible risks and its release may be delayed by years.

A series of drug-safety scandals has led many on Capitol Hill to question whether the **Food and Drug Administration** has failed to strike the right balance between speed and safety. A clear sign of this imbalance, these critics say, is the increasing number of **F.D.A.** drug-safety officers who say they have been punished or ignored after uncovering dangers of popular medicines.

The latest to suffer this fate is Dr. Rosemary Johann-Liang, 42, who recommended more than a year ago that the diabetes drug Avandia carry the agency's strongest possible safety warning for its effects on the heart.

Dr. Johann-Liang spent Friday sadly winding down her nearly seven-year career at the **F.D.A.** She turned in her BlackBerry, laptop and office key, and she went to the agency library to make sure she had no overdue books. She wished her colleagues well.

A pediatrician and expert in infectious diseases, Dr. Johann-Liang joined the agency in December 2000 and rose through the ranks. For four years, she reviewed drug applications as a medical officer and then team leader.

Two years ago she became a deputy division director in the agency's office of surveillance and epidemiology, the group that examines the safety of already-marketed drugs.

In February 2006, one of her safety reviewers, Lanh Green, went to her with a problem. The agency's Office of New Drugs had asked Ms. Green to determine whether eye problems that sometimes resulted from taking Avandia and a similar drug, Actos, were a serious issue. But Ms. Green noted that visual deficits were just one part of a drug-induced swelling problem that could lead to weight gain, ankle swelling and, if left untreated, heart failure.

Alerts about some of these problems were scattered throughout the two drugs' labels. Ms. Green suggested consolidating them and highlighting the heart risks

with a boxed warning, the agency's most severe. After a weeklong review, Dr. Johann-Liang agreed.

"There's no doubt these problems are caused by these drugs, and there's no doubt that patients are continuing to suffer bad outcomes," Dr. Johann-Liang said.

A week later, top officials from the new drug office walked by Dr. Johann-Liang's office and into the office of her boss, Dr. Mark Avigan, she said. Nearly an hour later, she said, the door opened, the officials left and Dr. Avigan called her in.

"Mark told me that they were upset with our recommendation," Dr. Johann-Liang recalled. "They decided to act like the review never happened."

Dr. Avigan took over the supervision of the safety review of Avandia and Actos and told Dr. Johann-Liang that she could no longer approve strong safety recommendations without his say-so, she said. Over the next year, she was increasingly excluded from crucial safety reviews and meetings, which contributed to her decision to leave the agency on Friday, she said.

In an interview, Dr. Avigan said that he did not intend to punish Dr. Johann-Liang.

"My view was simply that when there were conversations going on about important safety issues that were likely to garner a lot of attention, that I needed to be in the loop," he said.

On Wednesday, the **F.D.A.** commissioner, Andrew C. von Eschenbach, announced that the agency had asked for boxed warnings on Avandia and Actos, more than a year after Dr. Johann-Liang's recommendation.

At least four other **F.D.A.** safety reviewers in recent years have been punished or discouraged after uncovering similar drug dangers, according to Congressional investigations. Among them:

In 2003, Dr. Andrew Mosholder discovered that antidepressants led some children to become suicidal. When his findings were leaked to a reporter, the agency began a criminal investigation. Dr. Mosholder was prevented from speaking to an advisory committee about his analysis, and the agency hired Columbia University researchers to reanalyze the data; they concluded a year later that Dr. Mosholder had been right.

In 2006, Dr. David Ross became increasingly concerned about reports of serious illness and death from patients taking the antibiotic Ketek. Dr. Ross met with top agency officials and pleaded with them to take action. Nothing happened, he said. A month later, Dr. Ross complained privately to Congressional investigators. After articles about Ketek's safety problems appeared in The Wall Street Journal and The New York Times, the agency and Ketek's maker, Sanofi-Aventis, agreed to take actions.

After the articles were published, Dr. von Eschenbach held a meeting with Dr. Ross, Dr. Johann-Liang and other safety officials in which he urged them to keep their disagreements "inside the locker room," Drs. Ross and Johann-Liang said.

Those who discussed issues with outsiders would be "traded from the team," Dr. Eschenbach said, according to Drs. Ross and Johann-Liang.

Dr. Ross left the agency in November for the Department of Veterans Affairs. Dr. von Eschenbach later told a Congressional panel that he had intended his remarks to Dr. Ross and others to encourage scientific debate.

Senator Charles E. Grassley, Republican of Iowa, said Drs. Johann-Liang, Mosholder and Ross were part of a pattern demonstrating the need for reforms at the **F.D.A.**

Heidi Rebello, an **F.D.A.** spokeswoman, said that the "**F.D.A.** is not aware of any kind of retaliation," and that staff members "are committed to respecting all legal rights and protections of our employees."

In interviews, safety reviewers said problems at the agency could be traced back to a deal struck in 1992.

In the 1980s, the **F.D.A.** took nearly three years to approve most drugs. The AIDS crisis demonstrated that such long delays could condemn to death patients who might have been helped by recent scientific breakthroughs. **F.D.A.** managers said they did not have enough people to assess reviews more quickly.

So in 1992, Congress helped the **F.D.A.** and the drug industry reach a deal. Companies agreed to pay millions of dollars in fees, and the **F.D.A.** guaranteed that drug reviews would be completed within a year or as little as six months for a life-saving medicine.

At the time, it seemed a good solution. But the deal's fine print soon came to haunt the agency. Drug makers refused to let their money pay for the routine monitoring of drugs' safety once they were on the market. As the agency began to depend more and more on industry fees, those parts of the agency slowly withered.

Perhaps even more important, the culture at the **F.D.A.** shifted toward valuing speed over safety. The 1992 deal required annual reports to Congress listing review times, but no such reports were demanded of the agency's assessments of the safety of drugs already on the market.

Managers are now largely judged on how quickly their employees make a decision on new drug applications, safety officials say. Questions about the safety of already-marketed drugs are increasingly seen as sand in the gears, they say.

Drs. Johann-Liang, Ross and two other safety officials said Congress should require the **F.D.A.** to make regular public assessments of the safety of approved medicines, act on reports of drug problems within a month or two, and require regular reports on the agency's adherence to these goals. Such requirements would lead to the promotion of safety-conscious managers, not just speed-conscious ones, they said.

The Senate last month passed a bill to overhaul the **F.D.A.** that includes more money for drug-safety assessments and requires an advisory committee to meet

twice yearly to consider safety issues. The House will hold hearings on the legislation this week.

The safety officials say the bill does not go far enough, because it does not require clear timelines for a response to safety issues. It also does not require regular public disclosure of **F.D.A.** safety reviews.

"If managers were held accountable on safety issues, they'd pay more attention to them," said Dr. Victoria Hampshire, who was disciplined and investigated criminally in part because of her work to uncover the dangers of a heartworm medicine that killed at least 500 dogs.

Dr. Hampshire, who still works at the **F.D.A.**, said employees in Dr. Johann-Liang's former office were "very demoralized."

"There's a feeling of fear," she said.