ASSESSING THE SAFETY OF OUR NATION'S DRUG SUPPLY

HEARING

BEFORE THE

SUBCOMMITTEE ON HEALTH

OF THE

COMMITTEE ON ENERGY AND COMMERCE
HOUSE OF REPRESENTATIVES

ONE HUNDRED TENTH CONGRESS

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ASSESSING THE SAFETY OF OUR NATION'S DRUG SUPPLY

WEDNESDAY, MAY 9, 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 Waxman, Towns, Eshoo, Green, DeGette, Capps, Schakowsky, Solis, Matheson, Dingell, Markey, Deal, Buyer, Pitts, Ferguson, Rogers, Murphy, Burgess, Blackburn, and Barton.

Staff present: Ryan Long, Chad Grant, John Ford, Virgil Miller, Bobby Clark, Jack Maniko, Melissa Sidman, Lauren Bloomberg, and Nandan Kenkeremath.

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

Mr. PALLONE. Today the subcommittee is holding a hearing to assess the safety of our Nation's drug supply, and I feel very strongly that today's hearing is long overdue. For far too long, the subcommittee has not paid enough attention, I think, to the issue of drug safety, despite the growing concerns that the health and well-being of millions of Americans may be at risk due to a broken and inadequate drug safety system.

In recent years, there have been a number of revelations about drug safety that have shaken public confidence in the FDA's ability to ensure that consumers have access to safe and effective medications. From Vioxx to Paxil, tens of thousands of patients have been placed in harm's way due to the failings of our current drug safety system. And as a result, the American people have steadily begun to lose faith in the FDA. That should change.

We must restore public confidence in FDA's ability to protect people from harmful products and to safeguard the public health. But first, the FDA itself must change. There are a number of issues we must consider as we move forward. First and foremost, FDA is woefully underfunded. This was highlighted, as you know, in the hearing that we had a couple weeks ago on the reauthorization of PDUFA. More money is necessary for FDA to carry out its responsibility to protect consumers from harmful drugs.

However, it is an issue of where that money is going to come from. And obviously there is a lot of debate. There is growing concern regarding the increasing amount of user fees that FDA relies on to fund its budget. And as I have said before, if given the option, I think everyone would agree that FDA should be funded more, if not entirely, by annual appropriations. But realistically speaking, we are not in a place where we can't rely on user fees to help support the functions of the FDA.

That is not to say that we should give the drug industry carte blanche on how these fees should be applied. FDA should have more flexibility about what functions these monies can be used for, such as postmarket and surveillance.

For far too many years, the focus of FDA has been to approve the amount of time it takes to improve new drugs. And this is, of course, a direct result of previous PDUFA agreements in which industry provides a new revenue stream to FDA and in exchange establishes benchmarks for a more timely drug approval process.

Unfortunately, however, this has caused an imbalance between the pre-approval process and the post-market monitoring of drugs. We have to fix this imbalance and focus more of our attention on what happens with drugs once they reach the marketplace. Assessing the risk of the drug once it is on the market is just as important, if not more, than before it is approved.

Now, how are we going to achieve a more robust post-market drug safety system? Fortunately, we seem to already have many of the answers. First, we need to give the FDA greater authority and flexibility to manage the risks associated with a new drug once it has been approved. Currently FDA has little authority to control how a drug is marketed and how the risks and benefits are communicated to consumers.

FDA should have more options to mitigate the risks consumers face from a particular drug other than pulling it off the market entirely. Let us give the FDA the ability to require label changes, should it deem them necessary. Similarly, FDA should have the authority to require, as a condition of approval, that manufacturers follow through on their commitments to conduct and publish phase-four trials.

Even more important is ensuring that information about the clinical trials, including the results, is made public. It makes no sense that we would allow such information to remain locked away at the discretion of the industry. If my Republican friends are keen on transparency in the health care market, as they say, then let us start with full transparency of clinical trials. Let the consumers and their doctors decide what they think is safe or not based on complete information. The results of these clinical trials contain valuable information for patients and their physicians, and we should demand that they be made available.

Finally, I want to voice my concern about direct-to-consumer advertising. I realize that this is a very contentious issue, and I appreciate the industry and FDA's willingness to work out a compromise, which was included in this year's PDUFA proposal. However, as I said a couple of weeks ago, I am not certain that the new program outlined in the PDUFA proposal will suffice.

The fact that the program relies on voluntary participation from the industry strikes me as a program with no teeth. I am skeptical of these advertisers and the alleged value they bring to consumers. We will have to look at this program further and ensure that consumer's best interests are being served well.

There are many other issues that need to be discussed as we talk about drug safety. That is why today's hearing is an important one. And like I said at the beginning of my statement, it is long overdue that we have these hearings. I am looking forward to hearing from today's witnesses, and I thank you all for being with us and now recognize my friend from Georgia, Mr. Deal, for an opening.

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

Mr. DEAL. Thank you, Mr. Chairman. Thank you for holding this hearing today on an issue that certainly will be a component of our discussions on other FDA-related legislation that comes before our committee this year. Recent incidences, such as the recall of Vioxx that highlighted the importance of FDA's role in evaluating the safety of products both pre- and post-market, these events undermine consumers' confidence in the safety of medications they are taking and remind us that, while drugs provide useful life-saving treatment, there are risks associated with any medication.

In February 2005, the FDA announced the creation of a new independent drug safety oversight board to oversee the management of drug safety issues and provide information to help providers and patients about the risks and benefits of medicines.

I hope that our witnesses will be able to tell us about some of the work this board has been doing to monitor drug safety in addition to the FDA's other drug safety efforts. I also look forward to hearing about the role of databases in studying drug safety. I believe one of these studies was instrumental in highlighting that Vioxx increased the risk of heart disease. Studies like these show promise and demonstrate some of the possibilities for the FDA make use of existing drug data.

I want to thank our witnesses for their time and attendance today, and I look forward to your testimony as we evaluate the best means for ensuring patients have access to safe medications. Thank you, and I yield back.

Mr. PALLONE. Thank you, Mr. Deal. Mr. Waxman.

OPENING STATEMENT OF HON. HENRY A. WAXMAN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Mr. WAXMAN. Thank you, Mr. Chairman. I want to applaud you for holding this hearing today, for taking up the issue of drug safety at an opportune time. The Prescription Drug User Fee Act, or PDUFA, must be reauthorized this year, and everyone knows that in the end, it will pass. There is no realistic argument that it won't.

So we have a vehicle that will move, and as recognized in the administration's own PDUFA proposal, this vehicle could serve as a means to strengthen FDA's oversight of drug safety. We need to ensure that FDA not only has the ability to collect fees that help to

finance its oversight in our drug supply, but it also has the authority it needs to do this job well.

There is recent and mounting evidence that FDA's ability to oversee drug safety is a pale shadow of its ability to review drugs before they are approved. We are familiar with the series of post-market safety problems in the past year with drugs like Vioxx and Ketek. They demonstrate beyond a shadow of a doubt that FDA's post-market drug safety oversight is in serious need of repair.

The Institute of Medicine, the GAO, have examined this situation. Both concluded that FDA cannot protect Americans from unsafe drugs unless Congress provides more resources and more legal authorities. For example, right now, FDA cannot require post-market safety studies, even when FDA believes they are necessary to fully understand the drug's risk. FDA's only choice is to ask a company to perform these studies and hope they will agree. And in the case where the companies do commit to doing the studies in advance, if they don't do it, the only option is to take the drug off the market completely, which is a very serious one called a nuclear option, in fact. It is too tough for FDA to actually pursue.

According to the FDA's own figures in 2006, manufacturers submitted only 11 percent of the 1,200 open study commitments. 71 percent of these studies hadn't even started. The FDA also can't compel companies to make labeling changes after approval, as the case of Vioxx illustrates. FDA must haggle with companies, often for many months on end about the wording that should be used to notify the public about what are often very serious risks associated with taking their drugs. And throughout this process, the American public continues to take these drugs without any knowledge of these risks.

I have my own ideas for drug safety. Congressman Markey and I have introduced a bill, which incorporates the recommendations of the IOM and GAO. It is a counterpart to the drug safety legislation being debated on the floor of the Senate this week as part of its consideration of PDUFA. H.R. 1561 represents the blueprint for what we should be working on to fix the FDA's ailing drug safety system. I hope the committee will have an opportunity to consider it.

Thank you, Mr. Chairman.

Mr. PALLONE. Thank you, Mr. Waxman. Mr. Buyer.

Mr. BUYER. I will waive my time.

Mr. PALLONE. The gentlewoman from California, Mrs. Capps.

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

Mrs. CAPPS. Thank you, Mr. Chairman, and thank you for having this hearing, as others have said. I thank our witnesses for being here. I know the issue of drug safety has to be front and center as we discuss ways to go forward with PDUFA reauthorization. It is vitally important for the millions of people who depend upon pharmaceuticals and reasonably assume that they will do no harm.

FDA is charged with the responsibility to ensure that there are safe and effective drugs, and that is the purpose of our hearing today, to discuss ways to ensure that this responsibility is fulfilled. Drug safety must be addressed before clinical trials and continue

not only through the approval process but extend to post-market activity as well.

In the pre-approval period, we have to make sure that clinical trials are conducted with the highest scientific and ethical standards, ensure also that the members of the advisory committees, who make such important decisions about drug approvals, are free of ties to the industry.

The FDA has taken a supposed first step in this direction. I understand they have proposed a regulation which prohibits voting advisory committee members from holding more than $50,000 in stock in a drug before being considered or any of its competitors.

But do we really believe that goes far enough? Certainly we know that it hasn't yet been implemented. We must have confidence that drug approval decisions are based on scientific data, not on financial interests. As my colleague has mentioned, the high profile cases of Ketek and Vioxx and many others were fateful reminders about the importance of post-marketing studies and data collection.

I also hope we can discuss direct-to-consumer advertisements. It is a great concern to me that so many consumers who are patients rely on these ads and that proper oversight of their content does not exist. Perhaps most importantly, I believe we must equip the Food and Drug Administration with adequate resources. User fees have been instrumental in reducing drug approval time, but we must make sure that fees do not make up such a large proportion of FDA funding that it becomes a conflict of interest.

So I thank you, Mr. Chairman, again for holding this hearing. I look forward to ways in which we can work together to improve drug safety. I yield back the balance of my time.

Mr. PALLONE. Thank you. Mr. Ferguson.

Mr. FERGUSON. Thank you, Mr. Chairman. I am going to waive my opening statement for additional time in questioning, but I do just want to welcome constituent and friend Lisa Van Syckel. She will beon the second panel today. I am delighted that she is here today. I know she has several folks with her, including Ellen Liversage and Vera Sheral and Kim Witsack also here with her today. And because of the many, many meetings that she and I have had talking about drug safety over the course of the last several years, I have become very involved in the medication guide issue. We have been doing an investigation in our office and working with FDA and others. So I am looking forward to getting into that today, and I will look forward to using my extra time during questioning. I yield back.

Mr. PALLONE. Thank you. Ms. DeGette. I didn't count that. I guess I should have. Yes, we are going to have to watch——

Mr. FERGUSON. I think I am owed a little latitude by a chairman from my home State.

Mr. PALLONE. I will do better in the monitoring this in the future. Ms. DeGette.

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

Ms. DEGETTE. Thank you, Mr. Chairman. I think it is important that as we prepare to mark up legislation affecting regulation of pharmaceuticals and biologics that we put the safety of patients as paramount. And so I know these drugs will save countless lives, but we have to do what we can to mitigate unintended harm.

I really have three concerns today. The first one has been mentioned by several of my colleagues, and that is how we can make systemic changes to the FDA to make sure that they are really approving drugs that are safe. And our own investigations of Vioxx and Ketek as well as a number of other drugs over a period of years have shown that we really can't have that confidence that the safety is paramount.

The second issue that I have is that the FDA just really doesn't have the resources to adequately address drug safety concerns. And the most PDUFA agreement provides a significant increase in resources for post-market surveillance, but the fact remains that Congress still has to provide additional funds.

Also because of the drug safety problems, the American public has lost faith in the FDA and its ability to protect them from adverse effect. And this problem has been exacerbated by the ambiguous nature of the drug safety process. The general lack of transparency to the American public means that they don't see how decisions are made, and therefore they don't see why the drug companies are accountable to the FDA.

And finally, the full Senate is currently considering legislation to reauthorize PDUFA as well as a seemingly endless array of other drugs included in it. Though watered down, the Senate bill includes drug reimportation. Those of you who read the New York Times this last weekend saw the front page article that should make us all think twice about that policy. According to that article, counterfeit drugs made in China were exported to Panama for sale, and they included a deadly toxin. Last year, 365 families reported deaths as the result of the tainted cough syrup and fever medication. And they think that that number is vastly underreported.

Mr. Chairman, the dangers from counterfeit and contaminated drugs are frighteningly real, even under the current construct. Permitting reimportation would significantly increase the risk of counterfeit, misbranded and adulterated drugs that would end up in my constituents home. I hope we keep this in mind as we mark up-

[Applause.]

Ms. DEGETTE. I might have to take that back given the response from the other side. But seriously, I hope we keep this in mind as we mark up legislation on prescription drugs. If we have a problem with drug prices being too high in this country, we need to confront that problem head on and not allow reimportation policies that may affect the efficacy and safety of our drug supply in this country.

Mr. PALLONE. OK, now we have applause. Our ranking member of the full committee, Mr. Barton.

OPENING STATEMENT OF HON. JOE BARTON, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS

Mr. BARTON. Thank you, Mr. Chairman. It is good to have this hearing. I just got back from the trilateral committee hearing in Ways and Means where we had Ways and Means, Financial Services, and Energy and Commerce. Their opening statements will go on until about 5:00 this afternoon, I guess. So it is good to be here with one committee and one subcommittee and focus on one subject.

We do appreciate this hearing today. When I was full committee chairman of this august committee, I took the issue of drug safety very seriously. I am glad to see that Mr. Dingell and Mr. Pallone are continuing this. I requested a Government Accountability Office review of how the FDA approaches issues related to drug safety. I am looking forward to hearing from that agency today about what steps it has taken to improve the safety of our drug supply.

Where action is needed to improve drug safety, I think that Congress should be prepared to act. I do hope that we do it right instead of just in a hurry. I can testify personally that the development of new prescription drugs have revolutionized medicine and is saving lives.

Forty years ago, a person who had a heart attack like I had a year and a half ago would have been given nitroglycerin, a pat on the back, and sent home. Now, modern pharmaceuticals can help prevent attacks from occurring or even reoccurring. I know because each morning when I get up, I take six prescription drugs before I begin my day.

We must take steps to ensure that the drugs that we are taking are safe when they are approved and remain safe as they are put into commercial use. No drug can be 100 percent safe for every person who might take it. Even aspirin, the ubiquitous miracle drug that does everything from curing headaches to stopping heart attacks, has to be avoided by some people.

No responsible authority insists on absolute 100 percent safety because that standard would have the reverse effect of increasing the likelihood that many people would suffer or even die because they didn't have access to that particular drug.

As a drug used in the general population, less common side effects may be evident. Congress could impose Draconian new regulations that provide marginal benefits so that we appear to address the problem. What we would actually be doing in that case, in my opinion, is severely limiting access to life-saving drugs for tens of thousands or hundreds of thousands of people, lives that might be lost without that particular drug.

The history of drug regulation in this country reflects a conscious weighing of the drug's risks versus the drug's benefit. If more needs to be done to bring this balance into equilibrium, this Congress and this committee should and must explore those options, but we should never lose sight that millions of Americans depend on these medications to preserve and improve their lives.

Twenty-first century medicines must come with 21st century surveillance. Our health care system produces large quantities that can and should be used to monitor drug safety issues. We should have systems in place that can link up clinical data with prescrip-

tion drug use. Pre-market clinical trials are useful to determine the safety and efficacy profile of a drug, but if rare side effects occur, they must not become known until after the drug has been taken by a larger population.

It is my understanding that the FDA has begun to use clinical databases as a methodology to monitor safety concerns. I believe we should enhance that ability to tap into the existing health information. I am pleased that the agreement on Reauthorization of Prescription Drug User Fee Act will provide the FDA the ability to obtain access to additional drug safety information, including population-based epidemiological data and other types of observational data resources. I look forward to hearing from the FDA on their efforts in this area.

I also am looking forward to hearing from the testimony of Mr. John Theriault who will discuss the issue of prescription drug counterfeiting. It is shocking and unacceptable that the maximum penalty for counterfeiting a prescription drug in this country is 3 years in prison. Three years in prison. Phony drugs are the ultimate bad medicine. Impurities in the counterfeit drugs pose dangerous consequences for patients, and intentionally giving a serious ill person a drug that does not contain the active ingredients that they think it does could actually be considered to be murder.

Addressing counterfeit drugs requires public and private entities working together. Unfortunately, our anti-counterfeiting drug problems are not nearly as smart as the counterfeiters are. A first step to address the problem would be for the House to pass Congressman Rogers' legislation to substantially increase the criminal penalties for drug counterfeiters.

Second, we should look at new technologies that will allow us to better track these drugs in our supply system. I look forward to hearing from the company Pfizer about what steps that they are taking in this area.

Again, Mr. Chairman, thank you for holding this hearing. I look forward to participating.

Mr. PALLONE. Thank you, and I will recognize 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 holding this important hearing. The committee is here today to discuss the safety of our Nation's drug supply. And included in that is the competence and ability of FDA to carry out its very important mission.

The question here is what does it mean to say that a drug is FDA approved. Good government would say that the Food and Drug Administration approval should be the gold standard throughout the world, that the drugs approved provide needed therapies for consumers without causing further medical complications or worse, death.

Unfortunately, Food and Drug approval of pharmaceuticals as the gold standards has been called into question. Incidents highlighted by the recall of the arthritis drug Vioxx have created a crisis of confidence in the Food and Drug Administration.

It should be observed, however, that problems with Food and Drug go more broadly than this. It is an agency which has inadequate resources, inadequate numbers of personnel, inadequate financial support, and inadequate ability to carry out its responsibility, over both drugs manufactured and food manufactured in this country, and over imports, something which has shaken my confidence in a very real way in the agency.

I publicly express my dissatisfaction with the way in which Food and Drug has handled the important issue of drug safety. FDA's lack of transparency and recent recalls have greatly contributed to the loss of public confidence. The agency must aggressively monitor and assess safety and efficacy throughout the entire life cycle of a product. Simply stated, FDA must ensure that just as much time, resources and energies are invested in the aggressive post-market observation as is spent in pre-market trials, consultation, and meetings with the industry.

Unfortunately, it appears that there is a singular lack of resources at Food and Drug to carry out these responsibilities as it is to carry out other important responsibilities of that agency. A recent Institute of Medicine report concluded FDA and the pharmaceutical industry do not consistently communicate safety concerns in a timely and efficient and effective manner.

In addition to insisting on structural and resource changes within the agency, the country must also see to it that FDA continues to push for significant improvements in cultural changes at that agency. Public health policy is ultimately a human enterprise, and all facets of FDA's drug programs must work in a coordinated fashion for a common purpose, thereby ensuring consumers that the drugs they take are safe and effective. Again this will require a cultural change, but more importantly, it is going to require adequate funding and support for the agency which it currently lacks.

FDA has taken steps to boost consumer confidence. In 2004, they introduced a new drug safety initiative that promised to promote a cultural of openness and enhanced oversight within the agency. And it has included additional drug safety provisions in its recent PDUFA proposal.

The agency also asked the Institute of Medicine to evaluate its current system of drug safety and make recommendations for improvement. The Government Accountability Office, GAO, has also weighed in, and in 2006, released a report on FDA's ability to ensure a safe drug supply. The report included a number of recommendations. I am pleased that a representative from GAO is here to discuss this report. We will also want to discuss it with representatives of FDA and of higher officials in the Department of Health and Human Services.

It is, I think, appropriate that we should appreciate these efforts, but it is not clear to me that they, when coupled with the budget shortages of the agency, are sufficient. We are here today to see what additional steps that Congress may need to take so that American citizens are protected and the confidence in the agency is restored.

I appreciate this hearing, and I look forward, Mr. Chairman, to the testimony of our witnesses and the input of our members as we discuss the safety of the U.S. drug supply and the reasons why it

is not as safe as it should be and what steps we will take to improve it. Thank you, Mr. Chairman.

Mr. PALLONE. Thank you, Chairman Dingell. The gentleman from Texas, 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 frankly about the referenced aspirin, I guess I can't help but wonder if we were to send aspirin now through the Food and Drug Administration process if it would survive the approval studies or whether it would survive the post-market surveillance.

But this is a good hearing. This is an important panel of witnesses. I believe that we must strive to seek a balance between the safety measures that we put in place, at the same time allowing and facilitating new drugs coming to market. I believe that the FDA has done a good job with the resources available to it, but we can make it better. And Chairman Dingell may be correct about the allocation of resources.

Senator Mike Enzi from Wyoming has made a reasonable start to this discussion over in the other body by introducing his bill. His legislation would bring the risk/benefit analysis in at the beginning of the drug approval process. It would facilitate a lifetime approach to drug evaluation through the establishment of a drug safety oversight board.

Senator Enzi's bill also addresses two topics that are of particular interest to me, the critical path initiative and the establishment of databases. The critical path initiative strikes me as having great potential to fundamentally improve the way that we approve new drugs by utilizing the science that the research has yielded. If we could make our approval process more personalized, more efficient, safer, and faster, than I certainly support this.

In reading the materials supplied by the general accountability office, they raise a question what safety action that the FDA lacks—or rather they raised the point that the FDA lacks the information about what safety actions to take and when to take them. I believe that additional databases and data mining can help utilize information that is already available but needs to be collected properly. This can be helpful whatever we are examining, whether we are looking at the results from clinical trials or searching for adverse drug events through, for example, the Permanente patient population.

Data mining and rapid learning techniques are tools that are available but not being used to their full potential. Mr. Chairman, there is lots of information out there. It is a time of rapid change in the medical field. Going on *clinicaltrials.gov* Web site this morning, you can see that they have had 143 new hits during last week alone. And that is the pace at which information is coming into the FDA. This deals with illnesses as varied as asthma and appendicitis, pulmonary hypertension, and magnetic therapy for depressed adolescents. Innovative therapies must reach the clinical applicability stage with greater speed, but there also has to be the collection of data, the utilization of that data, and the post-marketing stud-

ies. Data collections should be available to arrive with greater speed and clarity for the clinician.

Finally, I do have to agree with my colleague from Colorado about reimportation. If the debate is over cost, then let us be honest and have that debate. Don't reimport drug price controls from countries who refuse to participate in paying for the research and development of those products in the first place.

Thank you, Mr. Chairman. I will yield back my time.

Mr. PALLONE. Thank you. The gentlewoman from California, Ms. Solis.

OPENING STATEMENT OF HON. HILDA L. SOLIS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Ms. SOLIS. Thank you, Mr. Chairman, and good morning. I am very pleased that you are having this hearing today and have an opportunity to talk about this important issue. Hundreds of millions of Americans rely on FDA's judgment regarding the safety of prescription drugs.

In 2005, the number of prescriptions purchased was about 3.6 billion, on an average, about 12.3 prescriptions per person. And FDA regulates daily 25 percent of gross domestic product and is sometimes called the largest consumer protection agency. It is critical that our consumers are actually being protected.

Each decision made by FDA is crucial and has life or death consequences for many of our constituents. In the past, drug safety may have been taken for granted. Patients have great trust and faith in FDA. However, the publicity surrounding many several drug recalls in the Institute of Medicine's report "The Future of Drug Safety: Promoting and Protecting the Health of the Public" shows that much work is needed to improve the safety of our medicines. The Institute of Medicine identified serious problems in monitoring drug safety and created numerous recommendations.

FDA has a difficult balancing act indeed. So I am pleased that FDA has taken the initiative to strengthen and improve the drug safety efforts. We know that FDA has to deal with external constraints, including significant funding gaps at the Center for Drug Evaluation and Research. However, FDA has a responsibility to evaluate and address the safety of prescription drugs after they have reached the market.

We must enable providers and patients to make the best possible decision about using medicines to improve their health. I have serious concerns regarding the transparency of the drug approval process, specifically adverse event reporting and the fact that FDA lacks authority to require that a manufacturer conduct a rigorous clinical trial to investigate post-market safety. Even if FDA requests a trial to be conducted, it has no way of enforcing the completion of that study. The fact that the completion rate of the post-market studies was less than 25 percent between 1991 and 2003 is disturbing.

The Adverse Event Reporting System is not an adequate drug surveillance system and does not capture all the adverse drug events. We need greater transparency and better communication in order to protect American consumers.

I thank the witnesses for coming today, and I look forward to hearing their recommendations, and I yield back the balance of my time.

Mr. PALLONE. Thank you. Mr. Rogers.

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

Mr. ROGERS. Thank you, Mr. Chairman. I have a long statement, and I would like to waive it at the end so that I can get more time in questions. Just kidding. If you are from New Jersey, you think that is funny, Mr. Chairman.

I want to bring your attention to an article published in The New York Times on May 6, 2007. It highlighted an investigation into the global and often deadly epidemic of counterfeit drugs. The investigation by the Times examined how counterfeit glycerin, a product often used in cough syrup, fever medication, and injectable drugs made its way via a poison pipeline stretching halfway around the world.

The counterfeit product was diethylene glycol, an industrial solvent and prime ingredient in antifreeze. Through shipping records and interviews, the counterfeit product from Panama was traced back through trading companies in Barcelona, Spain, a permitted country, I might add, under the legislation currently being considered—and back through Beijing, China.

Seventy years ago, when medicines laced with diethylene glycol killed more than 100 people in the United States. It led to the passage of the toughest drug regulations of that era and creation of the modern Food and Drug Administration. This creates an interesting contrast to the current debate over the potential drug safety and reimportation legislation. This has to be a component of that discussion, Mr. Chairman.

Last year, in Panama, 365 deaths were attributed to this poisoning with diethylene glycol in cough syrup. The World Health Organization estimates that global sales of counterfeit drugs were $32 billion in 2003. That is the last best year we have information. 10 percent of all those medicines sold worldwide, the value seized for counterfeit and diverted drugs in the United States alone was almost $200 million in 2003. And that was a sevenfold increase from the previous year.

Authorities have encountered significant difficulty in tying deaths to the actual consumptions of fake drugs mainly for the reporting system that is in place today. In Canada, it is currently investigating the death of a British Columbia woman, who died apparently after taking counterfeit pills she ordered online from what she believed was a Canadian Internet pharmacy. Officials have linked the death to pills purchased from this alleged Canadian Internet pharmacy about a month before she died. Her toxicology tests revealed that the counterfeit pills contained dangerous high levels of heavy metals strontium, uranium, and lead.

The World Health Organization estimates that 50 percent of the medicines purchased over the Internet from sites that conceal their address are counterfeit. This is a serious and growing problem, Mr. Chairman. The five top countries ranked for counterfeit incidents to the FDA are: one, China; two, Columbia; three, Russia; four,

India; and five, the United States. So I have introduced H.R. 780, a counterfeit drug protection act to strengthen the criminal penalties against those who participate in the production, distribution, and sale of counterfeit drugs, understanding the prevalence and dangers of counterfeit drugs is absolutely necessary, Mr. Chairman, in determining the safety of prescription medications in our Nation. And would yield back the remainder of my time.

Mr. PALLONE. Thank you. Mr. Towns.

OPENING STATEMENT OF HON. EDOLPHUS TOWNS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW YORK

Mr. TOWNS. Thank you very much, Mr. Chairman, for having this very important hearing today. Making sure that drugs are safe means making sure that they are safe for the diverse segments of our population as well. That simply is not the case. Minority participation in clinical trials has been cut in half over the last decade from 12 percent to 6 percent. And African-Americans represent less than 8 percent of those enrolled in cancer clinical trials, while Hispanics make up just 3 percent.

While pharmaceuticals are largely an effective means for addressing a wide range of health care needs, I am concerned that minority patients have not been adequately represented in many clinical trials. This means that as we seek to reauthorize the FDA, that we take into account the needs of diverse populations. To do this, we must increase the number of racial and ethnic minorities in clinical trials, particularly for diseases and conditions where there are health disparities.

This will increase public confidence in the FDA's ability to ensure drug safety. We must also make sure that the FDA itself is diverse. In addition, data from diverse populations must also be included in both pre- and post-marketing reports on safety and effectiveness to ensure that these studies look like America. Mr. Chairman, if we are to serve a diverse America, we cannot continue a one-size-fits-all approach to the development of new drugs and ensuring patient safety. Thank you, Mr. Chairman, for bringing this critical subject before us today, and I look forward to the testimony coming from the witnesses.

Mr. PALLONE. Thank you. Mr. Murphy.

OPENING STATEMENT OF HON. TIM MURPHY, A REPRESENTATIVE IN CONGRESS FROM THE COMMONWEALTH OF PENNSYLVANIA

Mr. MURPHY. Thank you, Mr. Chairman. The recent case, the tragedy at Virginia Tech, and actually the less publicized but equally problematic problems throughout our universities with mental health issues remind us that we have a large mental health problem nationwide that is not being adequately addressed. And when it comes to FDA and drug safety, and given my career as a psychologist, I want to emphasize some of the problems with this that I hope the FDA will address.

Today we are scheduled to hear some rather tragic testimony from a mother about her daughter, about some of the problems she had with antidepressant medication. And I want to emphasize this

for the FDA. That dealing with safe drugs is not just a matter of running clinical trials and posting more news in the PDA. It is also making sure that careful trials on adults and children and any of the population that will be using the medication is done, that research is ongoing, and that information is readily available and sent to all those who are prescribing the medications.

In the example of psychiatric medications, I find it disturbing to note that 75 percent of psychiatric medications are prescribed by non-psychiatrists. Even though we also know that a combination of medications with regular psychotherapy provided by trained licensed professionals is the most helpful, very often what happens with patients, they are given some medication and have little or no additional follow-up.

I believe it is critically important, whenever the FDA looks at approving drugs, they also make it absolutely clear under what context medication should be used, not only providing information on the use and side effects and regular and rapid updates to positions, but also making sure that information on the full context of treatment under which that medication is used is part of the prescribed regimen and not just the idea of handing off a pill.

It is also essential that messages continue to go out to the prescribers that clear communication must be ongoing with the parents when dealing with the pediatric population. Unfortunately we have set up so many barriers where parents are not aware of what is happening with their children's medication and with treatment, we are actually contributing to the problems of these children, and that is wrong.

Good health care has never been just a matter of taking a pill. Our culture, our whole health care system, has too often supported this past approach of take a pill and call me in the morning. We have to make sure that the FDA, in approving any medication, makes it absolutely clear the context that medication is prescribed and make sure that all involved are part of that communication system. And parents of the pediatric population, psychologists, psychiatrists, and others who are involved. Failure to do so will mean that more families will be harmed, and I hope that is one of the outcomes of what the FDA will be working on. Thank you.

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 first want to associate myself with the remarks of Mr. Towns, the clinical trials are to look like America. I know that women weren't included in cardiovascular trials until women were present in the Congress. And so now that we are a grand number of 72, I was surprised to hear at one of our last hearings that still the clinical trials, only 25 percent are women that are being tested. And yet we know already that there are great differences, as we know with African-Americans as well when it comes to cardiovascular disease and others.

I also wanted to talk about the approval process. The fact that it has been trimmed down from over 29 months in 1987 to cut in

half since then is a good thing for many people who are facing serious illness or chronic disease. But as we move forward with this conversation, it is very important to consider the other end of this approval process, the proposed approval process, which is essential to the health and safety of our constituents. If we accelerate pre-approval procedures, then tracking a drug in its post-approval lifespan becomes ever more important.

Relying on the current Adverse Events Reporting System, the AER System, is not sufficient. Not all adverse reactions are obvious to those who experience them. In cases like Vioxx, they only become apparent after months of use. Additionally a person won't always make the correct connection between a prescription drug and the side effect they are experiencing. Or they will fail to make any connection at all.

Furthermore, one has to consider how often a person or doctor will take the time to actually report a serious side effect. How many adverse effects are we missing with this process? We need to make sure that the right mechanisms are in place at the FDA to deal with these adverse events information in an efficient, objective, scientifically sound way and that the reported data is accessible to those who can use it to help avoid further incidents down the road.

One other concern I want to mention, we are relying on patients, many of whom are frail, elderly to understand complicated medical advisories, unclear directions issued by pharmaceutical manufacturers. Who is making sure that this information makes sense to them? Can they understand the relevant safety information on the drug inserts that come with their prescription medications? Is this information in the appropriate language? Are seniors and other relying on advertisements in the paper or able to read warnings that may be in four-point font? I am concerned with the dependency on adverse reporting to recognize post-market problems, troubled by the lack of oversight and authority on FDA's part to monitor the information on prescription drugs that is received or we think is received by those who need them. So I look forward to hearing from our witnesses, and I thank each of you for being here. I yield back.

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

OPENING STATEMENT OF HON. MARSHA BLACKBURN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TENNESSEE

Mrs. BLACKBURN. Thank you, Mr. Chairman. Thank you for the hearing, and I did want to say welcome to our witnesses. We do look forward to hearing from you, and we look forward to the information you are going to give us.

According to the GAO, the FDA lacks a clear and effective process for decision making about and providing oversight of post-market drug safety issues. I have often thought it would be interesting if the FDA were a patient to see what kind of diagnosis we would provide the agency.

The situation is exactly what my constituents complain about when they reference those bureaucrats in Washington, DC. We have two FDA offices functioning without clear guidelines and du-

plicating each other's work. And it is unfortunate that the Federal Government both allows and tolerates this kind of bureaucracy. And it is amazing that it comes at the risk of public safety.

I would hope that there are some best practices that someone is looking at implementing. Any private sector company would be out of business if they ran their business like the FDA runs the public's business. However, our drug review system is not totally broken, as many would believe, and sometimes it is as if we are trying to scare people to death by chipping away at the public's trust in this drug review process that we have. The U.S. has the best pharmaceuticals in the world and will continue to ensure that all drugs are properly vetted using the highest safety and review standards. And I hope that the FDA has the institutional will to reform their process and work toward restoring this trust.

While I understand the need for oversight and increased transparency in the FDA's drug review process, Congress should work toward a system with appropriate checks and balances. We must refrain from tactics, such as imposing a litany of needless regulation on the drug review system, which will prevent access to life-saving drugs. Expediency, transparency, efficiency should be a big part of the discussion.

As we continue to learn about drug safety issues, we must not forget that it is our duty to protect the public from unsafe drug approval and post-market review tactics.

I am looking forward to hearing from our witnesses. Mr. Chairman, I thank you, and I yield back.

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

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

Mr. GREEN. Thank you, Mr. Chairman, for holding this hearing on the safety of our drug supply. This hearing will complement this subcommittee's work on the Reauthorization of Prescription Drug User Fee Act as well as the Oversight and Investigation Subcommittee work on drug safety lapses at the FDA.

And the O&I subcommittee has uncovered serious problems with the FDA's handling of Ketek, antidepressants, and, of course, Vioxx. These cases have shed light on the structure and cultural and administrative problems at the FDA with regard to drug safety. They also have contributed to a decline in the American people's confidence in the FDA's ability to ensure the safety of our drug supply.

According to a Harris poll, 58 percent of Americans gave the FDA a negative rating when it came to public confidence, a number that has increased from 39 percent 2 years ago. To improve the public's confidence in the safety of our drug supply, there needs to be some big changes in the FDA. Some of the drug safety concerns can be addressed administratively at the FDA. I know that Dr. von Eshenbach has made significant effort to implement many of the Institute of Medicine's recommendations.

To correct other problems, however, the agency needs expanded authority from Congress. And it is our job to give the FDA the resources it needs to improve drug safety. We need to take a serious look at the Adverse Events Recording System and its ability to

identify adverse drug reactions following the drug's approval. The system is plagued with underreporting, and the FDA currently has a very high threshold for action. When taken together, these two factors unfortunately result in too many Americans being subject to harmful drugs for too long before the FDA steps in.

While the high profile cases make the nightly news, we know that problems continue beyond Vioxx, Ketek, and antidepressants. According to the GAO, 51 percent of all approved drugs have had at least one serious adverse drug reaction that wasn't caught during the approval process. There is no question we should be catching more of these adverse drug reactions before approval, but we should also have a robust post-market system that is nimble enough to recognize problems and act quickly to correct it.

Unfortunately, the scope that the FDA has authority to react is currently severely limited, and I hope that we change that in the PFUDA. If we are going to expand the FDA to ensure safety of our drug supply, they need to have the authority to require changes to drug labels when their scientists determine that black box warnings are necessary or that products should be restricted.

The FDA also needs the authority to enforce post-market study commitments made by drug manufacturers. With 71 percent of post-market study commitments not even begun by drug manufacturers, it is clear that the FDA lacks an enforcement mechanism with any teeth. Otherwise, the drug sponsor wouldn't show such blatant disregard for their post-market commitments to the FDA.

I would like to commend my colleagues, both Mr. Waxman and Mr. Markey for addressing many of these issues in their current legislation, a good portion of which is currently being considered on the Senate floor. I look forward to hearing from our witnesses on these issues and many others surrounding drug safety, and we appreciate their being here today. And I yield back my time, Mr. Chairman.

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 important hearing. I think that the issues that we are dealing with in this hearing are amongst the most important for the American people because there isn't a person in the country that, on their own, on their very own, can guarantee in any way, shape, or form that what they are taking, what they are ingesting is absolutely safe. They know that they have to depend on really the government and its blue chip agency, the Food and Drug Administration for it.

Now, we know that we have a problem, and it lies, I think, more in the post-marketing phase of drugs. The FDA actually does not have an active drug surveillance system. So I think now is the time. We are reauthorizing PDUFA, and we need to build in a process by which and an authorization, a direction for the FDA to actually have an active drug surveillance system.

The drugs that have caused problems or high profile Vioxx and Ketek, first of all, the agency has to have the funding to do this. I think that we have gotten to a point now where there is an over-

reliance on user fees. And the Congress has to step up to the plate to make sure that the agency has the resources it needs to carry out what, I believe, we need to do, and that is to set up a post-marketing drug surveillance system.

So I look forward to what the witnesses are going to inform us. I would like to thank publicly the IOM for the work that they have done on this. I think it has been useful and instructive to us. And I look forward to a reauthorization of PDUFA that is going to very clearly define the responsibilities for the FDA in this very particular area, as well as our recommendation relative to the resources for it. I think if we do one without the other, that it simply won't happen, and this is just too critical.

So thank you, Mr. Chairman. This is important, and we have had, since you have taken over as the chairman of this subcommittee, I think the hearings that we are having are the hearings that really matter on the most important things that are challenging us in the health arena. Thank you.

Mr. PALLONE. Thank you very much. I believe we are done with the opening statements, and any other statements for the record will be accepted at this time.

[The prepared statements of Mr. Allen and Mrs. Cubin follow:]

PREPARED STATEMENT OF HON. TOM ALLEN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MAINE

Mr. Chairman, thank you for calling for this important hearing to examine efforts to improve the current drug safety system.

I want to commend Representatives Waxman and Markey for their work on this issue and for the introduction of H.R. 1561, the Enhancing Drug Safety and Innovation Act, which will make the critical changes necessary to improve our current process for ensuring the safety and effectiveness of prescription drugs.

A pillar of U.S. policy on prescription drugs is the protection of the individuals who use them. Public confidence in our Nation's drug supply has been shaken in recent years by recalls of heavily marketed and widely prescribed drugs such as Vioxx. A new poll by Consumer Reports indicated that the vast majority of Americans want stronger drug safety laws and believe that more authority should be given to the FDA to protect consumers.

The Institute of Medicine report issued last fall offered 25 recommendations to improve the FDA's pre-approval processes. One of the most important recommendations, in my opinion, is the need for continuous safety monitoring throughout the life of the drug, including post-marketing surveillance.

The study found that "the FDA lacks the clear, unambiguous authority needed to enforce compliance with regulatory requirements and instead relies on the prospect of productive negations with industry."

This is troubling, and a clear indication that the system is broken.

I look forward to working with my colleagues to address this and other important issues; including improving public access to clinical trial results and ensuring that the FDA has adequate staff and funding to fulfill their mission to protect the public health.

I look forward to hearing the views of our distinguished panelists on ways to improve the current system to protect consumers from unsafe prescription drugs and restore their confidence in the FDA.

PREPARED STATEMENT OF HON. BARBARA CUBIN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF WYOMING

The Food and Drug Administration's safety activities are directly relevant to the everyday lives of every U.S. citizen. The 10,000 person agency is charged with monitoring roughly 124,000 firms that manufacture or process FDA-regulated products, which compose roughly one-fifth of our Nation's gross domestic product.

With this in mind, the notion that the public may be losing faith in the FDA's drug safety activities is unsettling at best. Over the last few years, the heavily pub-

licized removal of drugs from the marketplace has cast a shadow of public doubt over the FDA's ability to protect the American people from harmful products. 64,000 seniors in Wyoming now have access to affordable Medicare prescription drug coverage, but this means little if our drug supply is not safe.

In response to public and congressional concern, the FDA asked the Institute of Medicine to assess and make recommendations for our Nation's drug safety system, in addition to their own ongoing drug safety assessment. I am hopeful that today's testimony will help our committee understand both the extent of the safety reforms the FDA and industry have embarked upon, as well as steps that may need to be taken by Congress.

I would urge my colleagues to keep in mind that the FDA is charged not only with assessing drug safety, but also drug efficacy. These two prongs of the FDA's mission are not mutually exclusive, and should not be separated as we consider legislative changes to the agency's structure and authorities.

The agency does not just conduct risk management. It must also conduct risk-benefit analysis. Risk-benefit analysis can and should vary based on the severity of an illness and the availability of alternative therapies. We must consider the cancers and neuro-degenerative disorders for which patients have few, or even no, existing treatment options.

The acceptable risk for a drug treating mild arthritis will not be the same as for a drug treating Alzheimer's or Lou Gehrig's disease. There are seriously ill patients whose access to innovative treatments would be jeopardized by regulatory overreach, now matter how good intentioned. Their voices deserve to heard in this debate.

While I believe there is no one-size-fits-all regulatory solution for drug safety, there is no question that drug safety assessment should be based, to the greatest extent possible, on sound science.

Perhaps the greatest room for improvement in drug safety lies with post approval monitoring. Rare and serious side effects may not emerge until after a drug has been approved based on clinical trial data, in particular, drugs that treat smaller populations.

I hope today's panels will have suggestions for the tools and resources the FDA needs to conduct science-based, risk/benefit analysis throughout the market life of a drug. The dire need for innovative medicines among the seriously ill does not start and stop with the FDA's approval time-line, nor should serious efforts to ensure the health and safety of the American people.

Thank you Mr. Chairman. I yield back.

Mr. PALLONE. I will turn to our witnesses and ask the two for the first panel would come forward if you would. Now, let me introduce the two of you.

First, we have Dr. Steven Galson, who is Director of the Center for Drug Evaluation and Research at the Food and Drug Administration. And next is Dr. Marcia Crosse, Director of Health Care Issues at the U.S. Government Accountability Office. You have 5 minutes each. Your statements will be made part of the record, and you may, at the discretion of the committee, submit additional brief and pertinent statements in writing for inclusion in the record. And I will now recognize first Dr. Galson.

STATEMENT OF STEVEN GALSON, M.D., DIRECTOR, CENTER FOR DRUG EVALUATION AND RESEARCH, FOOD AND DRUG ADMINISTRATION

Dr. GALSON. Thank you very, very much, Mr. Chairman and members of the committee. I am Rear Admiral Steven Galson, FDA's director for the Center for Drug Evaluation and Research. I am very pleased to be here to talk about FDA's drug safety program and to reemphasize our continued commitment to drug safety.

As a physician, I have dedicated my career to serving public health. As a career medical officer in the U.S. public health service

since 1986, I have worked in the Nation's public health agencies to assess scientific data and make health recommendations and regulatory decisions that protect and promote the health of the American people. In my current position as director of CDER, I am deeply committed to leading an organization that inspires the trust and confidence of the people we serve.

My detailed testimony submitted for the record talks about the many initiatives CDER has on the way to strengthen drug safety. Modernizing the science of drug regulation, improving our internal operations, and enhancing our communications. I will focus my brief remarks today on describing my vision for the center and our vital role in protecting and promoting the public health with an increasingly complex health care system.

As you know, no drug is risk-free, and FDA plays a key role in assuring that a drug's benefits outweigh its risks, beginning with our determination whether a drug can be approved for marketing. And if so, ensuring that is it truthfully and adequately labeled.

Scientific progress is key to improving drug safety. CDER is meeting this challenge in many ways, including partnerships with outside groups who can assist us in developing new tools to improve safety. One example is an ongoing FDA scientific collaboration intended to yield better tests for toxicity than our current screening techniques. Such new tests would detect toxicity problems earlier in drug development than our current approaches.

Our responsibility continues, as you know, post-marketing when our programs identify adverse events not previously brought forward. To meet this challenge, CDER has taken a number of steps to strengthen the science that underpins these regulatory decisions. These scientific activities include developing and incorporating new tools to assess benefit and risk, upgrading our adverse event reporting system, and expanding our database resources. One example of the work we are doing to support the science of post-marketing drug safety assessment is exploring opportunities for linking private sector and public sector post-marketing safety monitoring systems to create a nationwide medical product safety network. Such a system could enable better safety information about medical products to get to health care professionals and patients at the point at which they are providing and receiving their care.

Communicating about marketed drugs is one of our key responsibilities, and health communications technology is rapidly evolving in this century. We too must change as this technology changes and improves. In this area, we have recently issued final guidance that describes our approach to communicating drug safety information, including emerging drug safety information to the public quickly, even if, in some cases, we are still evaluating this data.

Another part of improving our approach to drug safety is to listen to people outside FDA for ideas. Next month, on June 25 and 26, we will hold a public workshop to seek input from outside experts to discuss how risk management plans are working to enhance patient safety. In addition, we plan to establish a new advisory committee to obtain input on how to improve our external communications.

Lastly, I would like to address the steps we are taking to affect a culture change within CDER to become the kind of effective, effi-

cient and integrated center I am committed to leading. We are addressing tensions between our pre-approval and post-approval staff. We have enlisted the help of external experts to help to identify opportunities for improvement and assist us with implementation of these steps. We are examining ways to improve our handling and resolution of scientific disagreements.

CDER has employed process improvement teams to recommend changes to our drug safety program. A number of their recommendations have already been implemented, including the establishment of new safety-related positions in each of our drug review divisions and conducting regular safety meetings between groups.

We are also developing pilot projects to evaluate models of integrating our surveillance staff more into our drug review process, including having the staff participate in new drug reviews. We are firmly committed to ensuring that our surveillance staff have a strong voice pre- and post-marketing in safety decisions.

In conclusion, CDER's mission is to ensure that Americans have access to safe and effective drugs. Toward that end, our regulatory decisions must be based on sound science, applied with consistency and integrity. My personal commitment is to ensure that these decisions are informed by diverse points of view and vigorous academic debate.

We are committed to creating a comprehensive, systematic approach to improving the drug safety system, as quickly and efficiently as available resources allow. As always, we value input from Congress, the public, and the medical community as we develop and refine these drug safety initiatives.

Thank you for the opportunity to testify in front of the committee today, and I am happy to respond to questions after the next person. Thank you.

[The prepared statement of Dr. Galson follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

STATEMENT OF

STEVEN K. GALSON, M.D., M.P.H.

DIRECTOR, CENTER FOR DRUG EVALUATION AND RESEARCH

FOOD AND DRUG ADMINISTRATION

BEFORE THE

SUBCOMMITTEE ON HEALTH

COMMITTEE ON ENERGY AND COMMERCE

UNITED STATES HOUSE OF REPRESENTATIVES

May 9, 2007

RELEASE ONLY UPON DELIVERY

INTRODUCTION

Mr. Chairman and Members of the Committee, I am Rear Admiral Steven Galson, Director of the Center for Drug Evaluation and Research (CDER or the Center) at the Food and Drug Administration (FDA or the Agency). I am pleased to be here today to talk about FDA's drug safety program, and to emphasize our commitment to drug safety as part of our primary mission to protect and promote the public health. We have many initiatives already underway to strengthen the science of drug regulation, improve our internal operations, and enhance our communications with the public, health care professionals, and industry.

MODERNIZING DRUG SAFETY

As the Director of CDER, I play a significant role in helping to ensure the safety of drugs regulated by FDA. Drug safety has always been a key focus of my commitment to protect and promote the public health. In the past few years, the Center has reassessed many of its drug safety programs because of rapid advances in science and technology that have resulted in increasingly complex medical products. We take very seriously our response to safety-related issues raised by consumer advocates, health professionals, academic researchers, and Members of Congress.

For this reason, the Agency requested that the Institute of Medicine (IOM) convene an expert panel to assess the U.S. drug safety system and to make recommendations to improve risk assessment, surveillance, and the safe use of drugs. In addition to commissioning the IOM study in 2005, we initiated our own assessment of the drug safety program that continues

today. As part of that assessment, we received extensive input from external stakeholders and launched a number of initiatives that will enhance our abilities to review, monitor, and communicate about safety issues.

FDA has a strong safety record and remains the world's gold standard for drug approval and safety. We have maintained this record by taking actions to see what transformations are necessary to maintain and improve upon this standard. It is important to remember that no drug is absolutely safe. FDA approves drugs only after it is demonstrated that their benefits outweigh their risks for a specific population and a specific use, and that the drug meets the statutory standard for safety and efficacy. In other words, when we talk about drug safety, we are really talking about working to ensure a favorable benefit-to-risk balance for the drug when used by patients and to ensure that health care providers and patients have access to up-to-date information about the benefits and risks of a drug on which they can base their individual treatment decisions.

As the IOM report recognizes, resources are critical to improving our drug safety program. Both the President's fiscal year (FY) 2008 budget proposal and the Prescription Drug User Fee Act (PDUFA IV) proposal, include significant additional funding to modernize FDA's processes for ensuring drug safety. With the funds requested, FDA expects to strengthen the science and tools that support the product safety system at all stages of the product life-cycle from pre-market testing and development through post-market surveillance and risk management. FDA also expects to improve communication and information flow among all stakeholders. The FY 2008 Budget request and PDUFA IV funds would support FDA's

ability to effectively detect, communicate about, and act on important safety issues thereby improving patient safety and public confidence in FDA drug safety efforts.

FDA RESPONSE TO THE INSTITUTE OF MEDICINE REPORT

On September 22, 2006, IOM released its report *The Future of Drug Safety – Promoting and Protecting the Health of the Public*. The IOM report both recognizes specific progress and reform already initiated by the Agency and makes substantive recommendations about additional steps FDA can take to improve our drug safety program. In January 2007, FDA's comprehensive response to the IOM report described the Agency's commitment to strengthening our drug safety program as rapidly and efficiently as available resources allow. One of the driving forces for change is our ability to use the potential of emerging science and technology to develop useful tools to improve our drug safety programs. FDA is committed to a creating a comprehensive, systematic approach to improving the "drug safety system."

Our commitment has three interconnected themes: (1) strengthening the science that supports our medical product safety system, (2) improving communication and information flow among key stakeholders, and (3) improving operations and management to strengthen the "drug safety system." As Director of CDER, I have taken the lead in an aggressive effort to address and implement our response to the IOM's recommendations. We have made and will continue to make changes to our structure, policies, and processes to improve drug safety. I will discuss our IOM report response by highlighting the three themes of science, communications, and operations. In addition, I will discuss some of the significant changes and projects we are working on to improve drug safety in those areas.

1. Strengthening the Science

First, FDA is committed to strengthening the science that supports our medical product safety system at every stage of the product life cycle, from pre-market testing and development through post-market surveillance and risk management. We will focus our resources on three areas of scientific activity: (1) those relating to improving benefit and risk analysis and risk management, (2) surveillance methods and tools, and (3) incorporating new scientific approaches into FDA's understanding of adverse events.

One of our core functions is to continuously review post-marketing safety. Routine activities include reviewing many categories of information including adverse event reports, periodic safety reports, epidemiologic data, post-marketing clinical trial data, medical literature, information on other members of a class of drugs, and information from other sources to identify potential safety concerns. With the rapidly increasing number of adverse event reports that the Agency receives annually (fewer than 200,000 in 1996 and more than 470,000 in 2006), we are focusing on making our review processes more effective and efficient, using techniques such as data mining.

We have created a pilot program to look at selected New Molecular Entities after they have been on the market for a period of time (e.g., 18 months) to examine whether we can more rapidly and predictably detect problems in newly approved drugs. We are examining the analyses needed, the most efficient approaches to communicating and discussing the data, and how this systematic look compares to the review processes already in place. The results of

our experience with at least four drugs will be studied initially. Then the Agency will assess the pilot program for possible wider implementation.

In addition, we are implementing an electronic post-marketing safety tracking system to track and help manage safety issues. This system is already helping some CDER reviewers and managers to prioritize their work on safety issues and, when fully implemented, this system will replace multiple office and division specific systems.

We are working to strengthen surveillance methods and tools. We are in the process of upgrading the electronic Adverse Event Reporting System (AERS) by incorporating the latest tools, such as signal detection and tracking, and integrating medication error evaluation functions. This upgrade will make data more readily accessible to other public health agencies, research organizations, and the general public. We also are increasing safety database resources. Access to valuable data housed in large public and private databases will help us understand how the products we regulate are used by patients. Having these data available to our scientists will enhance their ability to detect and evaluate drug safety problems and medication errors.

In support of these functions, we are improving our data accuracy and completeness through measures including a renewed focus on registration of drug establishments and listing of their marketed products. This information is essential to identify drugs on the market and those who make them. It likewise allows us to link specific drug products to their approvals, labeling, and other critical information. We have proposed revisions to Title 21, *Code of*

Federal Regulations Part 207 (Registration of Producers of Drugs and Listing of Drugs in Commercial Distribution) that will mandate electronic registration and listing.

2. Improving Communications

FDA is committed to improving communication and information flow among all stakeholders to further strengthen the drug safety system. Open and transparent communication including rapid and effective dissemination of new information regarding safety issues among FDA, patients, and health care providers is key to promoting the safe use of medical products.

We plan to establish a new advisory committee to obtain input on how to improve the Agency's communication policies and practices, and to advise FDA on implementing communication strategies consistent with the best available and evolving evidence. We intend to include patients and consumers on the committee as well as experts in risk and crisis communication and social and cognitive sciences. The IOM report recommends legislation to establish this advisory committee, but we intend to implement this recommendation more expeditiously through administrative procedures.

We plan to conduct assessments of the effectiveness of identified risk minimization action plans (RiskMAPS) and current risk management and communications tools and to conduct public discussions on these issues. On June 25-26, 2007, we will co-host a public workshop with the Agency for Healthcare Research and Quality to seek input from outside experts from medical and pharmacy professional organizations, patient advocacy organizations, and others

to discuss how risk management plans are working to enhance patient safety. This meeting is another step towards that safety enhancement goal.

In March 2007, we issued final guidance that describes FDA's current approach to communicating drug safety information, including emerging safety information, to the public. The guidance affirms the Agency's commitment to communicate important drug safety information in a timely manner, including in some situations when the Agency is still evaluating whether to take any regulatory action. FDA's final guidance about the communication of drug safety information is available on FDA's website. We also plan to regularly publish a newsletter on FDA's website containing: (1) summaries of results of FDA post-marketing reviews, (2) information on emerging safety issues, and (3) information on recently approved products to inform providers and encourage reporting of adverse events to FDA. This newsletter will not include any confidential commercial or pre-decisional information.

3. Improving Operations and Management

FDA is committed to improving operations and management to ensure implementation of the review, analysis, consultation, and communication processes needed to enhance drug safety. It may be noted that approximately one-half of our daily work is safety related, and includes such diverse areas as assuring drug manufacturing quality over the product's lifecycle and human subject protection. Consistent with the IOM recommendations, we are implementing several reforms that, together, will improve the culture of safety at FDA.

CDER has initiated a series of changes designed to effect a true culture change that will strengthen operations and management. I have charged the members of my senior leadership team to lead the Center in an integrated manner that crosses organizational lines and they have taken steps to achieve this better integration.

CDER has reorganized in part to enhance our drug safety focus and to strengthen the integration of drug safety into regulatory decision making at all stages of the medical product life cycle. We have elevated the Office of Surveillance and Epidemiology (OSE) to report directly to me. In addition, I have established an Associate Center Director for Safety Policy and Communication to focus on the development and implementation of broad drug safety and communication policies. The person in this position serves as Chair of the Drug Safety Oversight Board and oversees that staff and the Medwatch staff. This position also reports directly to me.

In addition to CDER's own reorganization steps to enhance the drug safety focus of the Center, we have enlisted the help of external experts in organizational improvement. These external management consultants will help CDER develop a comprehensive strategy for improving CDER/FDA's organizational culture.

CDER has employed process improvement teams comprising staff in various organizations including OSE and the Office of New Drugs (OND) to recommend improvements in the drug safety program. The Center has implemented their recommendations to (1) establish an Associate Director for Safety and a Safety Regulatory Project Manager in each OND review

division within CDER and (2) conduct regular safety meetings between OSE and all the OND review divisions. We are committed to providing the necessary management attention and support to effect sustained culture change in our drug safety program.

FDA has initiated the development of two pilot projects to evaluate ways to involve OSE staff in reviews of drug and biologic applications. These include having an OSE staff person participate in each new drug application or biologic license application review, and other models for OSE involvement in post-marketing decision making. The Agency is committed to ensuring that OSE staff has a strong voice in pre- and post-marketing safety decision making. Furthermore, the proposed performance goals under PDUFA IV include provisions for enhancing and improving communication and coordination between OSE and OND.

In addition, we are committed to improving our use of advisory committees. In March 2007, FDA issued new draft guidance that would implement a more stringent approach for considering potential conflicts of interest for its advisory committee members and for recommending eligibility for meeting participation. FDA is currently accepting public comments on the proposal. The draft guidance is designed to make the advisory committee process more rigorous and transparent so that the public has confidence in the integrity of the recommendations made by its advisory committees. In addition, we are in the process of creating standard operating procedures for presenting post-market safety issues to an advisory committee. Furthermore, we plan to increase epidemiology expertise on our advisory committees.

PDUFA IV INCLUDES DRUG SAFETY ENHANCEMENTS

FDA proposes to use funds in PDUFA IV to help modernize and transform the drug safety system, throughout the entire life cycle of drug products. Our proposed enhancements include the activities and investments identified as most critical by our post-market review staff.

The recommended $87.4 million increase in drug user fees for FY 08 would include $29.3 million to support hiring of 82 additional staff for post-market safety activities as well as resources to support other important post-marketing drug safety activities. This would triple the amount of user fee funding available for post-market drug safety monitoring activities. We also propose to eliminate the current statutory time limit that restricts the use of user fees for drug safety activities to the first three years that a drug is on the market. This would allow user fees to fund safety activities on a marketed product at any time in the drug's life-cycle. Eliminating the statutory time limit will provide enhanced funding for the assessments of drug products over time, to adequately manage drug risks, regardless of a drug's approval date. FDA also would use the increased funds to further enhance and improve communication and coordination between FDA pre-market and post-market review staff, a key IOM recommendation.

In addition, as part of the proposed enhancements, we would analyze and adopt new scientific approaches to improve our tools for detection, evaluation, prevention, and mitigation of adverse events associated with drugs and biological products. We would use these increased funds to conduct research to determine the best way to maximize the public health benefits

associated with the collection and reporting of adverse events throughout a product's life cycle.

FDA would also use the proposed funds to identify and document epidemiology best practices, through input from academia, industry, and others in the public. This would inform our development of a guidance document that addresses epidemiological best practices and principles for the conduct of scientifically sound observational studies using quality data sources.

Another critical part of the proposed drug safety modernization would be maximizing the utility of current tools for adverse event detection and risk assessment. We would do this by seeking access to more and better data, such as population-based epidemiological data and other types of observational data resources. In addition, fees would support additional training for our current staff, and allow us to increase the number of professional staff who can review and analyze this safety information.

PDUFA IV also would allow us to develop a plan to evaluate current risk management plans and tools. We will 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 a $4 million increase in funding to improve the information technology (IT) infrastructure for human drug review, to move FDA toward an all-electronic drug review system. These infrastructure upgrades will allow us to implement a number of the IOM's recommendations to enhance drug safety. 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 AERS and surveillance tools.

In addition, FDA is proposing $6.25 million in new user fees for a voluntary program to review direct-to-consumer television advertisements for accuracy and balance prior to airing. This new program would support 27 additional staff with performance goals phased in over five years.

CONCLUSION

A core mission at FDA is to ensure that the American public has access to safe and effective medical products. We base decisions to approve a drug or to keep it on the market if new safety findings surface, on a careful balancing of risk and benefit, as well as consideration of the tools we have to help minimize the risks to patients from a drug's use. This multifaceted and complex decision process involves weighing both scientific and public health issues.

The recent initiatives we have announced will improve our current abilities to assess drug safety and to help assure that the drug products available to the American public are safe and effective. Moreover, we will continue to evaluate new approaches to advance drug safety. As always, we value input from Congress, the public, and the medical community as we develop and refine these drug safety initiatives.

Thank you for the opportunity to testify before the Committee today. I am happy to respond to questions.

Mr. PALLONE. Thank you, Doctor. Am I supposed to refer to you as Admiral or Doctor?

Dr. GALSON. Either.

Mr. PALLONE. Well, I guess we will stick with Doctor, I guess. And, Dr. Crosse, If you would give us your statement, thank you.

STATEMENT OF MARCIA CROSSE, DIRECTOR, HEALTH CARE ISSUES, U.S. GOVERNMENT ACCOUNTABILITY OFFICE

Ms. CROSSE. Mr. Chairman and members of the subcommittee, I am pleased to be here today as you examine the safety of the drug supply. My remarks today are based on GAO's March 2006 report on FDA's process for decision making regarding post-market drug safety and on steps FDA has taken that respond to the recommendations we made in that report.

Our work focused on two FDA offices that are involved in post-market drug safety: the Office of New Drugs, OND, and the Office of Drug Safety, ODS, which has since been renamed the Office of Surveillance and Epidemiology. Consistent with our report, I am referring to this office as ODS.

As we reported in March 2006, we found that FDA lacked a clear and effective process for making decisions about post-market drug safety issues. We found a lack of clarity about how decisions were made and about organizational roles. There was insufficient oversight by management. There were significant data constraints, and the agency lacked sufficient resources and authority to effectively ensure the safety of marketed drugs.

The decision-making process for post-market drug safety is complex, involving input from a variety of FDA staff, drug sponsors, the public, and many other information sources. Central to the process is the iterative interaction between OND and ODS, and many of the problems we identified derived from the ways these two offices managed their drug safety responsibilities. In particular, there was a lack of criteria for determining what safety actions to take and when to take them, which contributed to disagreements over decisions about post-market safety.

We found that insufficient communication between ODS and OND was an ongoing concern and hindered the decision-making process. For example, ODS did not always know how or whether OND had responded to safety analyses and recommendations for safety actions. ODS management did not systematically track information about the recommendations its staff made and OND's response. This limited the ability of ODS management to ensure that safety concerns were resolved in a timely manner.

Moreover, FDA faced data constraints that contributed to the difficulty in making post-market safety decisions. FDA's access to post-market clinical trial and observational data is limited. FDA does not have authority to require that a drug sponsor conduct a study for the purpose of investigating a specific post-market safety concern.

In the absence of such authority, FDA has relied on drug sponsors voluntarily agreeing to conduct these studies. However, as we heard, these studies have not consistently been completed. FDA was also limited in the resources it had available to obtain data from outside sources. Annual funding for this program was less

than $1 million a year for 2002 through 2005 and was $1.6 million in 2006, which allowed for four data contracts.

Today, just over a year after our report was issued, FDA has begun to take steps that could address the goals of three of our four recommendations to the agency. First, we recommended that FDA systematically track post-market drug safety issues, and the agency is in the process of implementing a tracking system.

Second, we recommended that FDA revise and implement its draft policy on the decision-making process for major post-market safety actions. And FDA has made revisions to, but not finalized, its draft policy.

Third, we recommended that FDA clarify ODS's role in scientific advisory committees, and the agency is developing, but has not finalized, guidance to clarify their role.

And fourth, we recommended that FDA improve its process to resolve internal disagreements, but FDA has not taken action in response to this recommendation.

In addition, we suggested in our 2006 report that Congress consider expanding FDA's authority to require drug sponsors to conduct post-market studies as needed to collect additional data on drug safety concerns.

In conclusion, while FDA has taken positive steps, its actions are not yet fully implemented, so it is too soon to evaluate their effectiveness in addressing these problems. Most importantly, the agency needs additional resources and authority to be able to fully address the range of post-market drug safety concerns.

Mr. Chairman, this concludes my prepared remarks. I would be happy to respond to questions that you or other members of the subcommittee may have.

[The prepared statement of Ms. Crosse follows:]

United States Government Accountability Office

GAO

Testimony

Before the Subcommittee on Health, Committee on Energy and Commerce, House of Representatives

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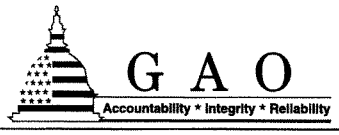
DRUG SAFETY

Further Actions Needed to Improve FDA's Postmarket Decision-making Process

Statement of Marcia Crosse
Director, Health Care



GAO-07-856T

May 9, 2007

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Highlights

Highlights of GAO-07-856T, a testimony before the Subcommittee on Health, Committee on Energy and Commerce, House of Representatives

DRUG SAFETY

Further Actions Needed to Improve FDA's Postmarket Decision-making Process

Why GAO Did This Study

In 2004, several high-profile drug safety cases raised concerns about the Food and Drug Administration's (FDA) ability to manage postmarket drug safety issues. In some cases there were disagreements within FDA about how to address these issues.

GAO was asked to testify on FDA's oversight of drug safety. This testimony is based on *Drug Safety: Improvement Needed in FDA's Postmarket Decision-making and Oversight Process*, GAO-06-402 (Mar. 31, 2006). The report focused on the complex interaction between two offices within FDA that are involved in postmarket drug safety activities: the Office of New Drugs (OND), and the Office of Drug Safety (ODS). OND's primary responsibility is to review new drug applications, but it is also involved in monitoring the safety of marketed drugs. ODS is focused primarily on postmarket drug safety issues. ODS is now called the Office of Surveillance and Epidemiology.

For its report, GAO reviewed FDA policies, interviewed FDA staff, and conducted case studies of four drugs with safety issues: Arava, Baycol, Bextra, and Propulsid. To gather information on FDA's initiatives since March 2006 to improve its decision-making process for this testimony, GAO interviewed FDA officials in February and March 2007, and received updated information from FDA in May 2007.

www.gao.gov/cgi-bin/getrpt?GAO-07-856T.

To view the full product, including the scope and methodology, click on the link above. For more information, contact Marcia Crosse, (202) 512-7119, crossem@gao.gov.

What GAO Found

In its March 2006 report, GAO found that FDA lacked clear and effective processes for making decisions about, and providing management oversight of, postmarket drug safety issues. There was a lack of clarity about how decisions were made and about organizational roles, insufficient oversight by management, and data constraints. GAO observed that there was a lack of criteria for determining what safety actions to take and when to take them. Insufficient communication between ODS and OND hindered the decision-making process. ODS management did not systematically track information about ongoing postmarket safety issues, including the recommendations that ODS staff made for safety actions. GAO also found that FDA faced data constraints that contributed to the difficulty in making postmarket safety decisions. GAO found that FDA's access to data was constrained by both its limited authority to require drug sponsors to conduct postmarket studies and its limited resources for acquiring data from other external sources.

During the course of GAO's work for its March 2006 report, FDA began a variety of initiatives to improve its postmarket drug safety decision-making process, including the establishment of the Drug Safety Oversight Board. FDA also commissioned the Institute of Medicine to examine the drug safety system, including FDA's oversight of postmarket drug safety. GAO recommended in its March 2006 report that FDA take four steps to improve its decision-making process for postmarket safety. GAO recommended that FDA revise and implement its draft policy on the decision-making process for major postmarket safety actions, improve its process to resolve disagreements over safety decisions, clarify ODS's role in scientific advisory committees, and systematically track postmarket drug safety issues. FDA has initiatives underway and under consideration and that, if implemented, could address three of GAO's four recommendations. In the 2006 report GAO also suggested that Congress consider expanding FDA's authority to require drug sponsors to conduct postmarket studies, as needed, to collect additional data on drug safety concerns.

Mr. Chairman and Members of the Subcommittee,

I am pleased to be here today as you examine the safety of our nation's drug supply. In 2004, several high-profile drug safety cases raised concerns about the Food and Drug Administration's (FDA) ability to manage postmarket drug safety issues. Those cases showed that there were disagreements and potential delays within FDA about how to address serious safety problems. My remarks today are based on GAO's March 2006 report on FDA's postmarket decision-making process (*Drug Safety: Improvement Needed in FDA's Postmarket Decision-making and Oversight Process*, GAO-06-402). I will also discuss a number of FDA's initiatives to improve its decision-making process, including some that respond to the recommendations we made in that report.[1]

In carrying out the work for our report between December 2004 and March 2006, we focused on two offices within FDA's Center for Drug Evaluation and Research (CDER) that are involved in postmarket drug safety activities: the Office of New Drugs (OND) and the Office of Drug Safety (ODS).[2] While there is some overlap in the activities of OND and ODS, they have different organizational characteristics and perspectives on postmarket drug safety. OND is involved in postmarket drug safety activities as one aspect of its larger responsibility to review new drug applications, and it has the ultimate responsibility to take regulatory action concerning the postmarket safety of drugs. ODS is primarily focused on postmarket drug safety, which includes the review of reports of adverse reactions to drugs. ODS operates primarily in a consultant capacity to OND and does not have any independent decision-making responsibility.

For our report, we interviewed ODS, OND, and other CDER managers and staff, as well as drug safety experts from outside FDA. We also analyzed documents describing internal FDA policies and procedures. In order to obtain an in-depth understanding of FDA's policies and procedures, we conducted case studies of four drugs—Arava, Baycol, Bextra, and

[1]The report is available online at www.gao.gov/cgi-bin/getrpt?GAO-06-402. See Related GAO Products at the end of this statement for other GAO reports about FDA's oversight of prescription drugs.

[2]ODS was renamed the Office of Surveillance and Epidemiology in May 2006. For the purposes of this testimony, we are referring to this office by its former name.

Propulsid—that help to illustrate the decision-making process.[3] Each of these drugs presented significant postmarket safety issues that FDA acted upon in recent years, and they reflect differences in the type of adverse event or potential safety problem associated with each drug, the safety actions taken, and the OND and ODS staff involved. To follow up with FDA about its responses to our recommendations and its initiatives to improve its postmarket safety decision-making process, we interviewed four FDA managers, including CDER's Associate Director for Safety Policy and Communication, in February and March 2007, and received updated information from FDA in May 2007. We did not evaluate the effectiveness of FDA's efforts to respond to our recommendations. All of our work was conducted in accordance with generally accepted government auditing standards.

In summary, we found that FDA lacked a clear and effective process for making decisions about, and providing management oversight of, postmarket drug safety issues. There was a lack of clarity about how decisions were made and about organizational roles, insufficient oversight by management, and data constraints. We observed that there was a lack of criteria for determining what safety actions to take and when to take them, which likely contributed to disagreements over decisions about postmarket safety. Insufficient communication between ODS and OND's divisions was an ongoing concern and hindered the decision-making process. For example, ODS did not always know how OND had responded to ODS's safety analyses and recommendations. ODS management did not systematically track information about the recommendations its staff made and OND's response. This limited the ability of ODS management to provide effective oversight so that FDA could ensure that safety concerns were addressed and resolved in a timely manner. FDA has faced data constraints that contributed to the difficulty in making postmarket safety decisions. In the absence of specific authority to require drug sponsors to conduct postmarket studies, FDA has often relied on drug sponsors voluntarily agreeing to conduct these studies. However, these studies have not consistently been completed. FDA has also had limited available resources to obtain data from outside sources.

[3]FDA approved Arava to treat arthritis; Baycol to treat high cholesterol; Propulsid to treat nighttime heartburn; and Bextra to relieve pain. Baycol, Bextra, and Propulsid have since been withdrawn from the market (in August 2001, April 2005, and March 2000, respectively), and the warnings on Arava's label were strengthened.

FDA has undertaken a variety of initiatives to improve its postmarket drug safety decision-making process. Prior to the completion of our report in March 2006, FDA commissioned the Institute of Medicine (IOM) to examine the drug safety system, including FDA's oversight of postmarket drug safety. FDA also established the Drug Safety Oversight Board in CDER and made other internal changes. Since March 2006, FDA has continued to address its oversight and decision-making shortcomings. In January 2007, FDA issued a detailed response to IOM's recommendations. In our 2006 report, we recommended that FDA revise and implement its draft policy on the decision-making process for major postmarket safety actions, improve its process to resolve disagreements over safety decisions, clarify ODS's role in scientific advisory committees, and systematically track postmarket drug safety issues. FDA has since begun to implement initiatives that we believe could address the goals of three of the four recommendations in our 2006 report. FDA has made revisions to, but not finalized, its draft policy on major postmarket drug safety decisions. FDA has not improved its process to resolve disagreements over safety decisions, and the agency is developing but has not finalized guidance to clarify ODS's role in scientific advisory committees. FDA is in the process of implementing a tracking system.

Background

Because no drug is absolutely safe, FDA approves a drug for marketing when the agency judges that its known benefits outweigh its known risks. After a drug is on the market, FDA continues to assess its risks and benefits. FDA reviews reports of adverse drug reactions (adverse events)[4] related to the drug and information from clinical studies about the drug that are conducted by the drug's sponsor. FDA also reviews adverse events from studies that follow the use of drugs in ongoing medical care (observational studies)[5] that are carried out by the drug's sponsor, FDA, or other researchers. If FDA has information that a drug on the market may pose a significant health risk to consumers, it weighs the effect of the adverse events against the benefit of the drug to determine what actions, if any, are warranted.

[4]Adverse event is the term used by FDA to refer to any untoward medical event associated with the use of a drug in humans.

[5]Observational studies can provide information about the association between certain drug exposures and adverse events. In observational studies, the investigator does not control the therapy, but observes and evaluates ongoing medical care. In contrast, in clinical trials the investigator controls the therapy to be received by participants and can test for causal relationships.

The decision-making process for postmarket drug safety is complex, involving input from a variety of FDA staff and organizational units and information sources, but the central focus of the process is the iterative interaction between OND and ODS. OND is a much larger office than ODS. In fiscal year 2005, OND had 715 staff and expenditures of $110.6 million. More than half of OND's expenditures in fiscal year 2005, or $57.2 million, came from user fees paid by drug sponsors under the Prescription Drug User Fee Amendments of 2002.[6] ODS had 106 staff in fiscal year 2005 and expenditures of $26.9 million, with $7.6 million from prescription drug user fees.

After a drug is on the market, OND staff receive information about safety issues in several ways. First, OND staff receive notification of adverse event reports for drugs to which they are assigned and they review the periodic adverse event reports that are submitted by drug sponsors.[7] Second, OND staff review safety information that is submitted to FDA when a sponsor seeks approval for a new use or formulation of a drug, and monitor completion of postmarket studies. When consulting with OND on a safety issue, ODS staff search for all relevant case reports of adverse events and assess them to determine whether or not the drug caused the adverse event and whether there are any common trends or risk factors. ODS staff might also use information from observational studies and drug use analyses to analyze the safety issue. When completed, ODS staff summarize their analysis in a written consult. According to FDA officials, OND staff within the review divisions usually decide what regulatory action should occur, if any, by considering the results of the safety analysis in the context of other factors such as the availability of other similar drugs and the severity of the condition the drug is designed to treat. Then, if necessary, OND staff make a decision about what action should be taken.

Several CDER staff, including staff from OND and ODS, told us that most of the time there is agreement within FDA about what safety actions should be taken. At other times, however, OND and ODS staff disagree about whether the postmarket data are adequate to establish the existence of a safety problem or support a recommended regulatory action. In those

[6]Pub. L. No. 107-188 § 501 et. seq., 116 Stat. 687.

[7]Health care providers and patients can voluntarily submit adverse event reports to FDA. Adverse event reports become part of FDA's computerized database known as the Adverse Event Reporting System.

cases, OND staff sometimes request additional analyses by ODS and sometimes there is involvement from other FDA organizations. In some cases, OND seeks the advice of FDA's scientific advisory committees, which are composed of experts and consumer representatives from outside FDA.[8] In 2002, FDA established the Drug Safety and Risk Management Advisory Committee, 1 of the 16 human-drug-related scientific advisory committees, to specifically advise FDA on drug safety and risk management issues. The recommendations of the advisory committees do not bind the agency to any decision.

FDA has the authority to withdraw the approval of a drug on the market for safety-related and other reasons, although it rarely does so.[9] In almost all cases of drug withdrawals for safety reasons, the drug's sponsor has voluntarily removed the drug from the market. For example, in 2001 Baycol's sponsor voluntarily withdrew the drug from the market after meeting with FDA to discuss reports of adverse events, including some reports of fatalities.[10] FDA does not have explicit authority to require that drug sponsors take other safety actions; however, when FDA identifies a potential problem, sponsors generally negotiate with FDA to develop a mutually agreeable remedy to avoid other regulatory action. Negotiations may result in revised drug labeling or restricted distribution. FDA has limited authority to require that sponsors conduct postmarket safety studies.

[8]These committees are either mandated by legislation or are established at the discretion of the Department of Health and Human Services (HHS).

[9]21 U.S.C. § 355(e). FDA may propose withdrawal when, for example, it determines through experience, tests, or other data that a drug is unsafe under the conditions of use approved in its application, there is a lack of substantial evidence that the drug will have the effect that it purports to have or that is suggested in its labeling, or required patent information is not timely filed. Prior to withdrawal, FDA would need to notify the affected parties and provide an opportunity for a hearing. Approval may be suspended immediately, prior to a hearing, if the Secretary of Health and Human Services finds that continued marketing of a particular drug constitutes an imminent hazard to the public health.

[10]At this meeting FDA communicated to the sponsor that it was considering proceeding with a withdrawal of the highest dose of Baycol because of its increased risk for a severe adverse event involving the breakdown of muscle fibers.

FDA Lacked a Clear and Effective Decision-making Process for Postmarket Drug Safety

In our March 2006 report, we found that FDA's postmarket drug safety decision-making process was limited by a lack of clarity, insufficient oversight by management, and data constraints. We observed that there was a lack of established criteria for determining what safety actions to take and when, and aspects of ODS's role in the process were unclear. A lack of communication between ODS and OND's review divisions and limited oversight of postmarket drug safety issues by ODS management hindered the decision-making process. FDA's decisions regarding postmarket drug safety have also been made more difficult by the constraints it faces in obtaining data.

Decision-making Process on Drug Safety Lacked Clarity about Criteria for Action and the Role of ODS

While acknowledging the complexity of the postmarket drug safety decision-making process, we found through our interviews with OND and ODS staff and in our case studies that the process lacked clarity about how drug safety decisions were made and about the role of ODS. If FDA had established criteria for determining what safety actions to take and when, then some of the disagreements we observed in our case studies might have been resolved more quickly. In the absence of established criteria, several FDA officials told us that decisions about safety actions were often based on the case-by-case judgments of the individuals reviewing the data. Our observations were consistent with two previous internal FDA reports on the agency's internal deliberations regarding Propulsid and the diabetes drug Rezulin.[11] In those reviews FDA indicated that an absence of established criteria for determining what safety actions to take, and when to take them, posed a challenge for making postmarket drug safety decisions.

We also found that ODS's role in scientific advisory committee meetings was unclear. According to the OND Director, OND is responsible for setting the agenda for the advisory committee meetings, with the exception of the Drug Safety and Risk Management Advisory Committee.[12] This includes who is to present and what issues will be discussed by the advisory committees. For the advisory committees (other than the Drug Safety and Risk Management Advisory Committee) it was unclear when ODS staff would participate.

[11]Rezulin was removed from the market in 2000 because of its risk for liver toxicity.

[12]ODS is responsible for setting the agenda for meetings of the Drug Safety and Risk Management Advisory Committee.

A Lack of Communication and Limited Oversight Hindered the Decision-making Process

A lack of communication between ODS and OND's review divisions and limited oversight of postmarket drug safety issues by ODS management also hindered the decision-making process. ODS and OND staff often described their relationship with each other as generally collaborative, with effective communication, but both ODS and OND staff told us that there had been communication problems on some occasions, and that this had been an ongoing concern. For example, according to some ODS staff, OND did not always adequately communicate the key question or point of interest to ODS when it requested a consult, and as ODS worked on the consult there was sometimes little interaction between the two offices. After a consult was completed and sent to OND, ODS staff reported that OND sometimes did not respond in a timely manner or at all. Several ODS staff characterized this as consults falling into a "black hole" or "abyss." OND's Director told us that OND staff probably do not "close the loop" in responding to ODS's consults, which includes explaining why certain ODS recommendations were not followed. In some cases CDER managers and OND staff criticized the methods used in ODS consults and told us that the consults were too lengthy and academic.

ODS management had not effectively overseen postmarket drug safety issues, and as a result, it was unclear how FDA could know that important safety concerns had been addressed and resolved in a timely manner. A former ODS Director told us that the small size of ODS's management team presented a challenge for effective oversight of postmarket drug safety issues. Another problem was the lack of systematic information on drug safety issues. According to the ODS Director, ODS maintained a database of consults that provided some information about the consults that ODS staff conducted, but it did not include information about whether ODS staff made recommendations for safety actions and how the safety issues were handled and resolved, such as whether recommended safety actions were implemented by OND.

Data Constraints Have Contributed to Difficulty in Making Postmarket Safety Decisions

Data constraints—such as weaknesses in data sources and FDA's limited ability to require certain studies and obtain additional data—have contributed to FDA's difficulty in making postmarket drug safety decisions. OND and ODS have used three different sources of data to make postmarket drug safety decisions, including adverse event reports, clinical trial studies, and observational studies. While data from each source have weaknesses that have contributed to the difficulty in making postmarket drug safety decisions, evidence from more than one source can help inform the postmarket decision-making process. The availability of these data sources has been constrained, however, because of FDA's

limited authority to require drug sponsors to conduct postmarket studies and its resources.

While decisions about postmarket drug safety have often been based on adverse event reports, FDA cannot establish the true frequency of adverse events in the population with data from adverse event reports. The inability to calculate the true frequency makes it hard to establish the magnitude of a safety problem, and comparisons of risks across similar drugs are difficult.[13] In addition, it is difficult to attribute adverse events to particular drugs when there is a relatively high incidence rate in the population for the medical condition. It is also difficult to attribute adverse events to the use of particular drugs because data from adverse event reports may have been confounded by other factors, such as other drug exposures.

FDA can also use available data from clinical trials and observational studies to support postmarket drug safety decisions. Although each source presents weaknesses that constrain the usefulness of the data provided, having data from more than one source can help improve FDA's decision-making ability. Clinical trials, in particular randomized clinical trials, are considered the "gold standard" for assessing evidence about efficacy and safety because they are considered the strongest method by which one can determine whether new drugs work.[14] However, clinical trials also have weaknesses. Clinical trials typically have too few enrolled patients to detect serious adverse events associated with a drug that occur relatively infrequently in the population being studied. They are usually carried out on homogenous populations of patients that often do not reflect the types of patients who will actually take the drugs. For example, they do not often include those who have other medical problems or take other medications. In addition, clinical trials are often too short in duration to identify adverse events that may occur only after long use of the drug. This is particularly important for drugs used to treat chronic conditions where patients are taking the medications for the long term. Observational

[13]This is due, in part, to the underreporting of adverse events and inconsistency in how those reporting define cases. These limitations have been reported elsewhere. See, for example, D. J. Graham, P. C. Waller, and X. Kurz, "A View from Regulatory Agencies," in Brian L. Strom, ed., *Pharmacoepidemiology* (Chichester: John Wiley & Sons, Ltd., 2000), pp. 109–124.

[14]In these trials, patients are randomly assigned to either receive the drug or a different treatment, and differences in results between the two groups can typically be attributed to the drug.

studies, which use data obtained from population-based sources, can provide FDA with information about the population effect and risk associated with the use of a particular drug.

We have found that FDA's access to postmarket clinical trial and observational data is limited by its authority and available resources. FDA does not have broad authority to require that a drug sponsor conduct an observational study or clinical trial for the purpose of investigating a specific postmarket safety concern. One senior FDA official and several outside drug safety experts told us that FDA needs greater authority to require such studies. Long-term clinical trials may be needed to answer safety questions about risks associated with the long-term use of drugs. For example, during a February 2005 scientific advisory committee meeting, some FDA staff and committee members indicated that there was a need for better information on the long-term use of anti-inflammatory drugs and discussed how a long-term trial might be designed to study the cardiovascular risks associated with the use of these drugs.[15]

Lacking specific authority to require drug sponsors to conduct postmarket studies, FDA has often relied on drug sponsors voluntarily agreeing to conduct these studies. But the postmarket studies that drug sponsors have agreed to conduct have not consistently been completed. One study estimated that the completion rate of postmarket studies, including those that sponsors had voluntarily agreed to conduct, rose from 17 percent in the mid-1980s to 24 percent between 1991 and 2003.[16] FDA has little leverage to ensure that these studies are carried out.

In terms of resource limitations, several FDA staff (including CDER managers) and outside drug safety experts told us that in the past ODS has not had enough resources for cooperative agreements to support its postmarket drug surveillance program. Under the cooperative agreement program, FDA collaborated with outside researchers in order to access a wide range of population-based data and conduct research on drug safety. Annual funding for this program was less than $1 million from fiscal year

[15]This was a joint meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee.

[16]Postmarket studies for approved drugs and biologics are included in the percent calculations. See: Tufts Center for the Study of Drug Development, Kenneth I. Kaitin, ed., "FDA Requested Postmarketing Studies in 73% of Recent New Drug Approvals," *Impact Report: Analysis and Insight into Critical Drug Development Issues*, vol. 6, no. 4 (2004).

2002 through fiscal year 2005. In 2006, FDA awarded four contracts for a total cost of $1.6 million per year to replace the cooperative agreements.

FDA's Initiatives to Improve Postmarket Drug Safety Decision Making

Prior to the completion of our March 2006 report, FDA began several initiatives to improve its postmarket drug safety decision-making process. Most prominently, FDA commissioned the IOM to convene a committee of experts to assess the current system for evaluating postmarket drug safety, including FDA's oversight of postmarket safety and its processes. IOM issued its report in September 2006.[17] FDA also had underway several organizational changes that we discussed in our 2006 report. For example, FDA established the Drug Safety Oversight Board to help provide oversight and advice to the CDER Director on the management of important safety issues. The board is involved with ensuring that broader safety issues, such as ongoing delays in changing a label, are effectively resolved. FDA also drafted a policy that was designed to ensure that all major postmarket safety recommendations would be discussed by involved OND and ODS managers, beginning at the division level, and documented.[18] FDA implemented a pilot program for dispute resolution that is designed for individual CDER staff to have their views heard when they disagree with a decision that could have a significant negative effect on public health. Because the CDER Director is involved in determining whether the process will be initiated, appoints a panel chair to review the case, and makes the final decision on how the dispute should be resolved, we found that the pilot program does not offer CDER staff an independent forum for resolving disputes. FDA also began to explore ways to access additional data sources that it can obtain under its current authority, such as data on Medicare beneficiaries' experience with prescription drugs covered under the prescription drug benefit.[19]

[17] A. Baciu, K. Stratton, and S. P. Burke, eds., Institute of Medicine of the National Academies, Committee on the Assessment of the U.S. Drug Safety System, *The Future of Drug Safety: Promoting and Protecting the Health of the Public* (Washington, D.C.: Sept. 22, 2006).

[18] The draft policy is entitled "Process for Decision-Making Regarding Major Postmarketing Safety-Related Actions."

[19] In October 2006, the Centers for Medicare & Medicaid Services published a proposed rule that would, when finalized, facilitate access by FDA and others to information about prescription drugs covered by Medicare. See 71 Fed. Reg. 61445 (Oct. 18, 2006).

Since our report, FDA has made efforts to improve its postmarket safety decision-making and oversight process. In its written response to the IOM recommendations, FDA agreed with the goal of many of the recommendations made by GAO and IOM.[20] In that response, FDA stated that it would take steps to improve the "culture of safety" in CDER, reduce tension between preapproval and postapproval staff, clarify the roles and responsibilities of pre- and postmarket staff, and improve methods for resolving scientific disagreements.

FDA has also begun several initiatives since our March 2006 report that we believe could address three of our four recommendations. Because none of these initiatives were fully implemented as of May 2007, it was too early to evaluate their effectiveness.

- To make the postmarket safety decision-making process clearer and more effective, we recommended that FDA revise and implement its draft policy on major postmarket drug safety decisions. CDER has made revisions to the draft policy, but has not yet finalized and implemented it. CDER's Associate Director for Safety Policy and Communication told us that the draft policy provides guidance for making major postmarket safety decisions, including identifying the decision-making officials for safety actions and ensuring that the views of involved FDA staff are documented. According to the Associate Director, the revised draft does not now discuss decisions for more limited safety actions, such as adding a boxed warning to a drug's label.[21] As a result, fewer postmarket safety recommendations would be required to be discussed by involved OND and ODS managers than envisioned in the draft policy we reviewed for our 2006 report. Separately, FDA has instituted some procedures that are consistent with the goals of the draft policy. For example ODS staff now participate in regular, bimonthly safety meetings with each of the review divisions in OND.

[20]HHS, FDA, *The Future of Drug Safety—Promoting and Protecting the Health of the Public: FDA's Response to the Institute of Medicine's 2006 Report* (Rockville, Md.: January 2007).

[21]The original draft policy included the market withdrawal of a drug, restrictions on a drug's distribution, and boxed warnings as major postmarket drug safety decisions.

- To help resolve disagreements over safety decisions, we recommended that FDA improve CDER's dispute resolution process by revising the pilot program to increase its independence. FDA had not revised its pilot dispute resolution program as of May 2007, and FDA officials told us that the existing program had not been used by any CDER staff member.

- To make the postmarket safety decision-making process clearer, we recommended that FDA clarify ODS's role in FDA's scientific advisory committee meetings involving postmarket drug safety issues. According to an FDA official, the agency intends to, but had not yet, drafted a policy that will describe what safety information should be presented and how such information should be presented at scientific advisory committee meetings. The policy is also expected to clarify ODS's role in planning for, and participating in, meetings of FDA's scientific advisory committees.

- To help ensure that safety concerns were addressed and resolved in a timely manner, we recommended that FDA establish a mechanism for systematically tracking ODS's recommendations and subsequent safety actions. As of May 2007, FDA was in the process of implementing the Document Archiving, Reporting and Regulatory Tracking System (DARRTS) to track such information on postmarket drug safety issues. Among many other uses, DAARTS will track ODS's safety recommendations and the responses to them.

We also suggested in our report that Congress consider expanding FDA's authority to require drug sponsors to conduct postmarket studies in order to ensure that the agency has the necessary information, such as clinical trial and observational data, to make postmarket decisions.

Mr. Chairman, this concludes my prepared remarks. I would be pleased to respond to any questions that you or other members of the subcommittee may have.

For further information regarding this testimony, please contact Marcia Crosse at (202) 512-7119 or crossem@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this testimony. Martin T. Gahart, Assistant Director; Pamela Dooley; and Cathleen Hamann made key contributions to this statement.

Mr. PALLONE. Thank you, Dr. Crosse, and we will start with the questions. I will recognize myself for 5 minutes, and I wanted to ask these questions of Dr. Galson.

In your testimony, you talked about all the things that FDA is doing in response to the IOM report. For example, you cite steps you have taken to improve communications and information flows as well as improve operations and management, especially between the Office of Surveillance and Epidemiology and the Office of New Drug. And I think these are positive steps that FDA has taken to reform itself administratively.

But as you know, there are some recommendations made by the IOM report that FDA can't do administratively. And I would like to know where the administration might stand on some of these recommendations. It is important for us to know where the administration stands as we move forward with reforming our drug safety system and whatever legislation we are going to put forward.

So I have three questions. Let me begin with the clinical trials. Does the administration agree with the IOM report that Congress should require industry sponsors to register in a timely manner at *clinicaltrials.gov*, at a minimum, all phase two through phase four clinical trials wherever they may have been conducted if data from the trials are intended to be submitted to the FDA as part a MBA, SMBA or to fulfill a post-market commitment? This goes on. Why or why not? And if Congress were to include this in our drug safety reform package, do you know whether or not the administration would object? That is my first question.

Dr. GALSON. Yes, as you know, provisions changing the way that we register and require registration of clinical trials has been part of the debate and the discussions going on in the Senate. And we are very actively participating in providing technical assistance to those provisions, and it has changed as time has gone by. We have supported some and not supported others, so we look forward to continuing the work——

Mr. PALLONE. I haven't necessarily followed the Senate. Sometimes we take pride in not following the Senate. Do you just want to comment, as best you can, on what you have been saying over there in this regard?

Dr. GALSON. We are very much in favor with providing as much transparency as possible, concerning clinical trials that are underway. There has been a huge amount of progress made over time in getting more of these trials registered, and I am sure you are going to hear more about this from the pharmaceutical representatives that are up here. But if you look on that Internet site now, there is a lot more information on there than it used to be, and we are in favor of that.

Mr. PALLONE. Well, what about the mandate though, the mandatory aspect?

Dr. GALSON. With regard to the specific provisions, we will continue to discuss that with staff, and the administration hasn't taken a firm position on exactly where we stand on each one of those provisions.

Mr. PALLONE. OK. Well, let me go to No. 2. The IOM recommended that Congress ensure that the FDA has the ability to require such post-marketing risk assessment and risk management

programs as needed to monitor and ensure safe use of drug products. They go on to recommend that FDA should have the ability to impose these conditions before and after approval of a new drug, as well as having increased authority and better enforcement tools, such as fines, injunctions, and withdrawal of approval to ensure compliance by drug sponsors. Are these recommendations something that the administration would support, and again why or why not with regard to the risk management assessment?

Dr. GALSON. Thank you. As you know, I am sure, there are risk management plans that are currently part of approval of a number of drugs that are on the market, and we thought them through very carefully. And after the drugs are on the market, we evaluate those plans to see whether they are working. This is another area we have been very active providing technical assistance to the Senate and other Members of Congress that are interested in talking about this. And we think when there are drugs that have special risks, they do require special attention and special risk management plans for the drugs to be approved and for us to carefully follow up afterwards.

Mr. PALLONE. But again in those cases, you have mentioned special cases, would you think the FDA should have the ability to require the risk assessment and the risk management in those cases?

Dr. GALSON. We don't feel comfortable approving drugs that have special risks, unless there is a way to manage that risk. And it is very much on a case-by-case basis that we make that assessment. We are concerned about a one-size-fits-all approach in the discussions that we have had with the Senate on this provision because the work is very time consuming for our staff. And we want the ability to focus our attention on the most pressing public health problems. So, in general, we haven't favored a one-size-fits-all approach but our ability to make a case-by-case assessment. And that could include, in some cases, being able to make sure that some studies get done.

Mr. PALLONE. OK, I have to ask one more question only because I didn't get a chance last time. This is about the new DTC user fee program that was included in PDUFA Four Proposal. That was negotiated between the FDA and industry. I wanted to ask this at the PDUFA hearing, but I ran out of time, and again I am running out of time. What assurances do we have that drug companies would actually participate in this new program, given that it remains voluntary? And would the administration support a program that requires all advertisements for new drugs be reviewed by the FDA?

Dr. GALSON. Again, this is a complex regulatory and legal area, and as you may be aware, there are a large number of television ads and, of course, even much larger number of printed materials that are produced by the pharmaceutical industry. And we have a fairly modest staff that is able to review those as it is. So again we are concerned that if we are asked to review more materials that we have adequate ability to do that, and that has been a challenge between the resources and the number of products that have come in.

What this new program does is give us additional staff so that we can do a lot more comprehensive job of looking at this particular subset as they come in. And we are very, very interested in

making sure that they are truthful and they are not misleading. And I suspect that the industry is interested in that as well.

Mr. PALLONE. So it is a question of money as always. All right, thank you very much. I yield to the gentleman from Georgia, Mr. Deal.

Mr. DEAL. Thank you. One of the issues that has come up before this subcommittee on other hearings as it relates to approval of products has been the question of where intellectual property rights become an impediment to making information more available.

With regard to clinical trials, both pre-approval and post-approval, one of the discussions has been to make more information about those clinical trials available to the public. Are intellectual property rights one of the constraints that you encounter in those environments? And if so, would you elaborate on that?

Dr. GALSON. Absolutely. One of the challenges in all the work that we do is having our scientists able to look at all the vast information that is available concerning products. We digest this. We evaluate it. We sometimes debate it, and in the end, we come out with assessments and communication that helps both practitioners and patients make the right decisions about risk and benefit.

Putting every single piece of information that may be in that drug company application down to the patient level does raise intellectual property issues. And we are obligated by our laws to protect the intellectual property, and I am not sure that it would really benefit patients as well because they don't want the undigested data. They want to know what is FDA's assessment of this data.

An additional point on that is that we do think very carefully about patients who need new products, patients who have cancer and other chronic conditions. And we don't want to do anything that is going to stand in the way of getting those products through the development process and evaluated by us in making those appropriate products available.

Mr. DEAL. One of the tools for post-market determinations and safety, of course, is in mining data that may be available. To what extent has the FDA utilized whatever resources, if any, might exist in mining data collected by CMS, since they have a huge bank of data? Has there been any correlation between the two agencies in that regard?

Dr. GALSON. Yes, there has. As you know and you have heard, some of the statements that you all have made have indicated the very, very exciting frontier really in drug safety—our ability to look at large data sets as they are being developed specifically, electronic medical records, more records from these larger payer databases, such as CMS. And as you all are very, very aware, the new provisions in Medicare drug benefit are going to make a lot more data available in the Medicare system that will allow us to link eventually medical outcomes with the drugs that are prescribed.

And to prepare for that very optimistic future of being able to use more of this data, we have been engaged in an interaction with the Medicare program, looking at the existing data to try to see how can we work with that and learn lessons with that interaction. We have been working with our sister agency, AHRQ as well, and I just got a briefing on this earlier in the week. And we are making

some good progress and hopefully will learn some lessons that will allow us to move forward as we get more funds from Congress to be able to use this data and hire our staff so we are prepared to mine any available data sets that are valuable for patients.

Mr. DEAL. Dr. Crosse, have you had the opportunity to look at what other countries are doing on post-market surveillance of drugs, and how does that compare with what we are doing in the United States?

Ms. CROSSE. Sir, I am afraid we have not done any recent work at all looking at drug safety systems in other countries. As you know, there are a number of differences in the review and approval process in those countries and also in the kinds of data that may be available to them because of the national health systems they have. But we have not done any recent reviews that would help you on that.

Mr. DEAL. Dr. Galson, with regard to imported drugs, does the law, as it is currently written, in your opinion, give FDA sufficient authority to deal with drugs that are actually manufactured in other countries? What are the limitations that you incur in dealing with those imported drugs?

Dr. GALSON. Right. I assume you mean the legally imported drugs that are part of our current system, and there is a significant portion of the drug supply that is currently manufactured by some of the same companies that are household names, but they happen to be manufactured overseas.

All of our requirements for drug approval generally apply for drugs that are imported, as they do here. So we go overseas, and we inspect foreign manufacturing facilities when those companies are importing their product to the United States. When clinical trials are done overseas and those clinical trials are used in our application process, we go overseas and inspect them. So we have good authorities to do that.

Mr. PALLONE. Thank you. Mr. Waxman.

Mr. WAXMAN. Thank you, Mr. Chairman. Dr. Galson, if you look at the drugs where there have been problems or drugs that have been withdrawn from the market, it looks like a pattern where the risks appeared before approval, and the agency got caught off guard. To fully address this trend, I think it is clear you need some help from Congress. You need more resources. You need more authorities. But within the confines of FDA's current authorities and resources, what are you going to do to fix this problem?

Dr. GALSON. That is a very challenging issue, and I think the first thing is we have to be very wary about looking backwards and trying to figure out what we may have done wrong in the past when the situation was very different back when you were looking at data initially, but your point is well taken. And I think the real future of improvements in drug safety lie in scientific areas, and we are very invested in that and our critical path initiative and talking to many of you working on projects with not just the industry but also with academic groups and non-profit organizations to try to make sure that the information that we are getting before approval gives us the best possible data so that we do a better job of being able to predict which drugs are going to work and which drugs are going to cause adverse events in other people. And so

that 10 years down the road, we will be able to stand on our laurels and say that these sort of surprises after approval have been avoided. Now, we do sometimes get signals before a drug is approved, as you said, that there may be a safety issue. And each time we see that, based on clinical trial data, we look carefully into that, and we try to make an assessment about whether that signal is going to result in a problem post-approval. The way to do a better job of that and to avoid what you are pointing out is better techniques, techniques like pharmacogenomics that will allow us to understand better individual differences between patients.

Mr. WAXMAN. In the meantime, there are problems that are discovered after the drug has already been approved. FDA asks the manufacturer if they would be willing to do a drug surveillance after approval. And especially if you have those signals, you want the manufacturer to do that because you think there may be a problem down the road. When FDA identifies, after a post-market survey, a need to change the drug's label, including adding a black box warning, can you describe the process FDA uses to compel a drug company to make a change? Can you compel a drug company to make that change?

Dr. GALSON. We feel pretty strongly that when we need a black box, or we feel like a drug has to be labeled better, either with a black box or another kind of warning for the drug to stay on the market—we have a very good process of sitting down with the company and saying look, there is this new information that has come out. We are really not comfortable——

Mr. WAXMAN. When you negotiate in this process with the company, that can take a long time, can't it?

Dr. GALSON. We are committed to reducing that time, and it has been reduced. And the other thing that we are doing related to that is that if there is not agreement there, we will go ahead—and we have done this in numerous cases over the last couple years. We will go ahead and put that information out without discussing it with the company. We will put out patient or physician information sheets. We will issue a public health advisory.

Mr. WAXMAN. But how about that label, even a black box label, if the company refuses as you are negotiating, and it takes months to negotiate. Meanwhile the public is unaware of these problems. If the company refuses to make the labeling change that FDA believes is necessary, what are your options? Isn't it just simply to take the drug off the market?

Dr. GALSON. We could take the drug off the market, but we push the companies, and in general, they respond. It doesn't take months, and once we say we are going to go out and put this information in the public realm, whether or not you move quickly enough, they usually move.

Mr. WAXMAN. Dr. Crosse, from what Dr. Galson has told us, it seems like he feels comfortable with the situation. Yet you made a recommendation that Congress provide FDA with the authority to require post-market studies and to be able to put these labels on and to insist that these studies be done.

Ms. CROSSE. Yes, sir. The information that we have reviewed over a number of years has found that it can be a lengthy process. I think it is a very positive step that FDA is now taking to more

publicly notify physicians and individual patients of concerns that have arisen. In the past, that was not their general practice. And so I do think that that is a positive step that the agency is taking to put the information out publicly if the company is not moving expeditiously to make these changes.

But our understanding is that the FDA's options are limited if the company is not cooperating. And while I agree that pressure can be brought to bear, and making this information public helps to bring that pressure, still the options available are quite limited if FDA feels that there is a positive benefit of this drug and that there are patients who need to continue to be able to receive it, and they don't therefore want to enforce the withdrawal from the market.

Mr. WAXMAN. Just a last comment. I know my time is up, but I am in a situation now where I am chairman of the Oversight Committee, try to get information to conduct investigations. But knowing that I have the authority to issue a subpoena doesn't mean I have to issue subpoenas. But it does mean that those who have to deal with me are more forthcoming. I would rather have FDA be able to deal from a position of strength rather than pleading for information, which they need and ought to have in order to protect the public health and to make sure the public is aware of the problems once they are discovered.

Thank you, Mr. Chairman.

Mr. PALLONE. Thank you. Mr. Barton.

Mr. BARTON. Thank you, Mr. Chairman. Back in August 2007, Mr. Whitfield and I wrote a letter to the Department of Justice, asking for them to review current law in terms of FDA authority with respect to imports of drugs both legally and illegally into this country. And their response back to us was this past December. And in that letter, the Assistant Attorney General, a Mr. Klinger, said that they, the Department of Justice, would support a change in the Food, Drug, and Cosmetic Act that would make sure that that Act gave the FDA explicit jurisdiction over conduct that occurs outside the United States for drug products that are subject to the Food, Drug, and Cosmetic Act when they are imported into the United States. I would assume that the FDA supports that. Is that correct?

Dr. GALSON. Yes, we do, as well as stiffer fines in those circumstances.

Mr. BARTON. And if we did give this authority, this explicit authority, how would the FDA and would that give the FDA the authority to inspect facilities overseas on a random, surprise basis like you have here in the United States? My understanding is when you inspect a pharmaceutical factory in China, you have to get permission before the fact and they actually announce sometimes 2 to 3 months in advance so that the day you show up, everything is sparkling clean and smiley-faced.

Dr. GALSON. I am not an expert at international comparative regulatory law; however, it is very important that we are able to go into foreign factories. The current situation is we do work with foreign countries, governments, when we make these visits. Even to get into many countries, they have to be aware that FDA officials are coming in.

On the other hand, we do do a lot of these inspections, and we send teams over, and they successfully inspect and identify problems. And those problems are addressed or we move forward to take the next step.

Mr. BARTON. In the United States, you can just show up and flash the badge, so to speak, and do the inspection. Isn't that correct?

Dr. GALSON. That is correct.

Mr. BARTON. But overseas, you can't do that. Is there any country that you can inspect as you do here in the United States? Or do you have to pre-clear it?

Dr. GALSON. I am happy to look into that to see whether there are any countries where we have the capacity to do that and get back to you.

Mr. BARTON. And on counterfeit drugs, what is the current status of trying to prevent the counterfeit drugs in terms of number of inspectors and things like that?

Dr. GALSON. We do focus some resources on counterfeit drugs, and we are very concerned about this. We work with pharmacies, with States, to move forward when we identify problems and to make sure that we have an open policy wherein people hear about counterfeit drugs. They are reported to us. We investigate it. We are concerned about counterfeits that are available on the Internet. And of course, if there are more drug imports coming in, that would be something we have to focus on more.

Mr. BARTON. Dr. Crosse, would you like to comment on any suggestions for combating counterfeit drugs?

Ms. CROSSE. Well, we had undertaken a review about 2½ years ago of Internet pharmacies, and we placed a number of orders from pharmacies over the Internet, both in the United States and in Canada and other foreign countries. We found a number of problems including counterfeit drugs. Some of the samples that we received were counterfeit medications, and a very small sample of drugs we purchased, out of about 63 purchases, we have four counterfeit drugs. And we had other drugs that were provided without any instructions for use, without appropriate labels or warning information or directions on how many tablets to take and at what interval. There are a number of difficulties that we identified in that review in the use of foreign pharmacies.

Mr. BARTON. But four of the 63 purchases were counterfeit?

Ms. CROSSE. Yes, sir.

Mr. BARTON. That is pretty amazing. Well, Mr. Chairman, my time has expired, but I hope that is something that, as we move forward, this whole issue of counterfeiting is, I think, a very great concern and based on what Dr. Crosse just said, I was assuming it was maybe 1 percent, 1 out of 100. But 4 out of 60 is—what is that—about 8 percent, something like that. So that is non-trivial. Thank you, Mr. Chairman.

Mr. PALLONE. Thank you. The gentlewoman from Colorado, Ms. DeGette.

Ms. DEGETTE. Thank you, Mr. Chairman. Following up a little bit on Mr. Barton's question. Dr. Crosse, I think the time is now to start looking at these counterfeit drugs because we had some hearings in the Oversight Investigation subcommittee in the last

Congress where customs is just seizing all kinds of these drugs coming in, and as Dr. Crosse described, they have no description what they are and when they are tested. Some of the drugs from South America were actually yellow paint, dyed paint. And there is no indication if the proper climate controls or other kinds of controls have been established.

And so I guess my question to you is what mechanisms do we currently have in the U.S. to expose counterfeit drugs before they reach a U.S. consumer? Do we have enough laws to do that, and maybe more importantly do we have enough resources to do that?

Dr. GALSON. Let me talk about a couple of the things that we have been doing. We have been focusing on this for quite a few years, but there is no doubt that this is something that probably needs more attention into the future. And you only have to open up the newspaper to see some of the problems that have occurred.

One of the things that we did is we were hearing that it was cumbersome for people to figure out how to report when they found a counterfeit or when they heard about a counterfeit. So we modified our standard adverse event reporting form that comes in to make it easier for people to explicitly say when they find a counterfeit.

Ms. DEGETTE. When did you modify that report?

Dr. GALSON. I believe it was 2005.

Ms. DEGETTE. And have you noticed an increased number of reports coming in?

Dr. GALSON. We haven't, but that probably reflects the fact that the adverse reporting system is not that sensitive.

Ms. DEGETTE. It has probably been the least effective way, waiting until the drug actually gets to the consumer. And then they have to make a report.

Dr. GALSON. Absolutely.

Ms. DEGETTE. So what else are you doing?

Dr. GALSON. Well, one of the things that does concern us, and we are going out with education efforts about this, is the increase of number of drugs that have been purchased over the Internet and the proliferation of Internet pharmacies and people thinking that this is an answer to getting their drugs. And clearly that makes it easier for people to get. Even if the drug is advertised that it is "from Canada" it may come from somewhere else.

Ms. DEGETTE. I know that, so what are those efforts?

Dr. GALSON. Those efforts are trying to communicate with people and with pharmacists and.

Ms. DEGETTE. And have those born fruit in finding additional counterfeit drugs?

Dr. GALSON. I don't think our detection of counterfeits is robust enough to really know whether——

Ms. DEGETTE. And so what do we need to do?

Dr. GALSON. Yes. Well, I think one thing is resources, and we do expect to be getting more resources under PDUFA that we will be able to put out in the field to detect more of these. As you know, there is just a sea of drugs coming in through the mail and through the borders. And it is a challenge for us to open up every single package. But there is more that we could do, and we will be focusing——

Ms. DEGETTE. Dr. Crosse, do you have any opinions what we could do to beef up our detection of counterfeit drugs coming in?

Ms. CROSSE. I think it is a very difficult issue for FDA alone to face because a lot of the drugs that are coming from the Internet pharmacies from overseas are coming directly to consumers.

Ms. DEGETTE. Right.

Ms. CROSSE. They are not passing through the normal drug supply chain in this country. And so, there really is very little, short of intercepting packages at the border, that FDA, I think, can do beyond these kinds of steps to monitor the pharmacies that are on the Internet. We found Web sites popping up and closing in a matter of days when we were undertaking our work. It is very difficult to track all of the Web sites that may be available to sell some of these drugs.

Ms. DEGETTE. So really consumer education will be important?

Ms. CROSSE. That is one of the steps, and certainly, I think there are some technological solutions that are being proposed to try to put in some sorts of tracers and other kind of tracking information that would allow the drug supply system to more adequately monitor when the drugs that are coming in are authentic.

Ms. DEGETTE. Now, do you think that this problem we have got right now would be exacerbated if more reimportation was allowed by Congress?

Ms. CROSSE. I am not aware of what the specifics are for proposals that are under consideration for the limits that we placed on that importation. In the small review that we did, we did not find problems with the drugs we purchased from Canadian pharmacies. But, as Dr. Galson has indicated, one cannot always determine just from looking at a Web site whether a site that identifies itself as being Canadian actually is.

Ms. DEGETTE. Dr. Galson.

Dr. GALSON. Yes. A couple points. The first is just following up on the technological solution. We do think that there are some technological steps, and these radio frequency identification tags, RFID, is one of the technologies that has been identified that can mark packages so they can be tracked and traced more efficiently. We have issued guidance on the use of this technology, and we are going to be putting more effort towards that. So that is a technological solution. On your question about importation, I don't think there is any question that if there are more drugs coming into the country from other places, it is going to be more difficult. And I think about my challenge in being responsible for all the currently legally imported drugs. If the number of manufacturing facilities and companies doubles or triples with drugs coming in from a lot more countries or from countries that are difficult for us to inspect, there is no question that it is going to be more of a challenge to detect these counterfeits and go out and inspect the sources.

Ms. DEGETTE. Thank you.

Mr. PALLONE. Thank you. The gentleman from Indiana, Mr. Buyer.

Mr. BUYER. I want to thank Ms. DeGette. I welcome her to this issue. This is a pretty strong concern of members on this committee. We reauthorized PDUFA, and we are now examining the postmarket review. I don't understand how a manufacturer out there

can do the very best they can, they are responsive to these reports of adverse effects that are being sent on, yet their ability to police the counterfeit—it is almost as if we have a system—so what do we have in America? We have got this system, and we have a leak. And the strength of the policing of that leak is going to come from who? Those whom have the most at stake. So it is going to come from, first would be the manufacturers themselves. They are going to protect because they have liability on the line. Second it is you, us, the Federal Government because we have given this assurance to the American people that we are going to have a closed system with regard to our drug supply, and that it is that FDA stamp of approval. It has got to mean something. So I think it is pretty clear. An unapproved FDA drug lacks your assurances of safety, effectiveness, quality, and purity. Now, if the FDA cannot assure the safety and efficacy of a drug product line because you can't gain access to the manufacturing process, we have serious problems.

So if that drug is manufactured in a foreign country and you gain access to that manufacturing process, there is not a problem there, and you do that all the time. In the mid 1990's, we had this political escalation and the attacks of our pharmaceutical manufacturers and as if well, just run off to Canada and get your drugs. And this reimportation issue began to erupt.

And then we see this increase in the volume of adverse event reports. So my question is do you know of any correlation between this increase in adverse reports and the amount of FDA unapproved drugs that are finding access into our country. Is there a correlation between this? Do you know?

Dr. GALSON. We are not aware of a correlation between those two. There are a number of hypothesized explanations for why that number is increased. One is there are more drugs out there. More people are taking more prescription products. If you look over time at the number of prescription drugs taken per person in the United States, it has gone up. And similarly there is absolutely more awareness of drug adverse events. I am not at all trying to say that there is no correlation, but I wouldn't want to blame that increase entirely on this issue.

Mr. BUYER. All right, let us bubbacize this. So last night, I picked up the phone and I called an internist, Dr. Lauren McClure in Muncie, Indiana, OK. Now, she is dealing with a problem because the mayor of Muncie, he is going to reduce the drug costs to the city of Muncie, Indiana. So what does he do? He instructs the city employees and the workers and the retirees to do what? Get their drugs from Canada. Now, as a practicing internist, she has a challenge. She will do her diagnosis, and in her prognosis, she will prescribe particular drugs. And she doesn't know what is working and what is not working and why.

So here we have someone that we as a country have invested greatly into this medical expertise, and it is a scratch of the head. She doesn't know whether the drugs the person is taking are FDA-approved drugs, or are these the counterfeit drugs? And so she has been challenged as she continues on. Now, this happens to be a doctor that actually knows that a patient is gaining access through Canadian pharmacies. How about if the docs all across the country, you prescribe a drug, and they don't even realize that their pa-

tients are out there. Ma'am, when you said I don't have a problem with Canadian pharmacies, what about these Canadian Internet sites? People think that they are approved, and many of them are unapproved, and they are the flow, the pathways of these illegal substances.

Now, our challenge is the person may not get better and die if it doesn't get reported. Those who say well, let us go to reimportation. People aren't dying from reimportation. You never know. So now if we want to make sure that we really understand about a drug that is out there, what do we in Congress need to do here? Do we have to mandate that doctors ask their patients that—I gave you that prescription. When you come back and you are not better, we ask them where did you buy your drugs? I hate to do something like that. Are we going to have to do that? And No. 2, when you talk about tools and modernization in the aftermarket, are you going to take into account the knowledge that we have about this escalation of the counterfeit drugs that are coming into the market? Those are my two questions.

Dr. GALSON. Yes. Well, we have identified one of our major goals in drug safety is to improve how we communicate to the public about drug risks, through the Internet, through other types of media, through medical organizations, other professional organizations, such as the pharmacists. There are other players in this, as you may know. The pharmacy world is regulated by and large by the State pharmacy boards, so talking to State people. And there is no question that we need to do more communication. We have a lot of activities underway in the agency focused on this, particularly warning people about Internet pharmacies and to get their drugs through a traditional source. But there is no question we could do more.

Mr. BUYER. Here is how you stop the mandate. How about you contact the AMA and through the continuing medical education, advising counsel with regard about asking that question. Where are you getting your drugs?

Dr. GALSON. Yes, we do work with the AMA.

Mr. BUYER. In medical schools?

Dr. GALSON. Yes.

Mr. BUYER. In the training? You work with the medical schools?

Dr. GALSON. We do some work with medical schools. That is an excellent idea.

Mr. BUYER. Let us do more with our medical schools and teaching so that they know it is part of their prognosis is what I would recommend, and the continuing medical education piece. And you can take that with you.

Dr. GALSON. Thank you.

Mr. BUYER. The last is on the increase in surveillance. I like the fact that you are checking our ports of entry and working properly with customs. So in PDUFA, if we want a purity with regard to that close market review sample, what in resources do we need to put in this bill? Tell me what you want and need to get the assurances of clients.

Dr. GALSON. Right, the FDA staff who are out in the field who are at the ports working with customs are not part of the drug center. It is a different part of the agency. I would be happy to go back

and ask them exactly to let you know what they think is needed to move forward here. We do provide technical and other kinds of compliances systems and work together with that group. And we are looking very much forward to additional resources coming in through the PDUFA program so that we can do more of this kind of assistance and participation in our compliance efforts.

Mr. BUYER. What agency is it?

Dr. GALSON. It is part of FDA. It is called the Office of Regulatory Affairs.

Mr. BUYER. All right, thank you. Thank you, Mr. Chairman.

Mr. PALLONE. Thank you. Recognize the gentlewoman from Illinois, Ms. Schakowsky.

Ms. SCHAKOWSKY. Thank you, Mr. Chairman. I wanted to ask Dr. Galson, you may have said this already. Maybe I missed it. The GAO suggested that Congress expand or consider expanding FDA's ability to require drug sponsors to conduct post-market studies, and so what is your view on that?

Dr. GALSON. Well, we have been working, as you know, with providing technical assistance to the committees in Congress and both sides that are working on issues of authority, so we will continue to do that. We do feel like we are able to get a lot of information post-marketing, and we are very committed to what we have talked about, improved surveillance by getting data sets and groups of data about drugs and how they are prescribed and the adverse events that may result through them that had nothing to do with even requiring drug companies to do studies. This is kinds of surveillance data that other groups, such as the health care payers—you are going to hear a little bit from them in the afternoon—that I think is the future of drug safety, looking at the databases that are out there.

Ms. SCHAKOWSKY. I understand you are talking about outside groups, but if we maintain a voluntary infrastructure on this in general, why would we as members of Congress or the public have confidence when we have seen so many problems with failure to report things and poor reporting of clinical trials and all kinds of things that the pharmaceutical companies have done? I mean I am trying to understand the source of your confidence when you emphasize this relationship with the private sector and pharmaceutical companies.

Dr. GALSON. Yes, a couple points. First is that what many people don't realize in the debate is that we can require some studies to be done in several different categories. The first of those are under the legislation that has promoted the development of more information about drugs for children, and we are able to require companies to do studies.

Ms. SCHAKOWSKY. How is it that many of them have been started but incomplete?

Dr. GALSON. In the pediatric area, I will get to that in a second. The other second area is the program that we have under our regulations called accelerated approval. When there is something that is really needed to fulfill a medical need, such as a cancer drug where there isn't another drug out there, we can approve the drug and then require a company to do a study after approval. And those studies do get done. And the third area is in the counter-ter-

rorism area where there is a drug that we think needs to be made available in case of a terrorist attack, but it wouldn't be ethical to do that study in humans. We can approve the drug using animals and then require a later study or a later collection of data.

But with regard to your main question, we are happy to continue to discuss it with this committee and with others your ideas for requiring more study to be done and give you our views on the specifics.

Ms. SCHAKOWSKY. Dr. Crosse, I wondered if you wanted to comment on that.

Ms. CROSSE. Yes, we do believe that FDA would benefit from having additional tools at hand to be able to take steps when they believe they were necessary and they were not getting voluntary cooperation. With regard to the pediatric studies, that certainly has promoted a number of drugs being studied for pediatric uses; however, almost 20 percent of those drugs that FDA asked to be studied, the sponsors declined to study for a variety of reasons.

But nevertheless, there still are a number of drugs out on the market that FDA had indicated were important for review. And it was at the option of the manufacturer whether to pursue those. The alternative path that the pediatric—and specifically Best Pharmaceuticals for Children Act—have provided for the Foundation for the National Institutes of Health to pursue the studies has not been effective. None of the drugs that have been referred for study by that organization have yet been studied.

Ms. SCHAKOWSKY. We have a problem here. I was intrigued by—both Dr. Crosse mentioned that there were some problems with the pre- and post-marketing divisions of the FDA. You called it tensions, Dr. Galson. Do we have to really deal with tensions here? I mean can you resolve those problems?

Dr. GALSON. Well, there is tension inherent in drug regulation, and I don't think we will ever get away with a totally stress-free easy job. And that is really not what I am looking for. And the fact is that two people looking at the same scientific data may come to different conclusions, and so it is not just between offices but even within the staff. And again this is normal, and the other regulatory and scientific agencies that I have worked in, you have had this same tension.

I am not meaning to diminish it or anything by calling it tension. It is part of the regular scientific debate when we make science-based decisions in public health agencies, and we have to do our best. And we are working to improve how we handle those disagreements to make sure that both sides are able to articulate their views and that we document our position in relation to those views and move forward and make our decisions.

Ms. SCHAKOWSKY. I am out of time. Thank you.

Mr. PALLONE. Thank you. Mr. Ferguson.

Mr. FERGUSON. Thank you, Mr. Chairman. Thank you both for being here, and thank you for your testimony. Dr. Galson, I have a lot I want to try and get through, and I am just going to try and get through it as quickly as I can. I appreciate your cooperation as well.

As you are aware, I have been interested in this issue of regulation and distribution of medication guides, med guides, for a while

now. I want to focus my time today on this alarming situation in which young patients and their parents may not be receiving the information that they need to make fully informed decisions about the treatment of certain medications, particularly including antidepressant medications.

Specifically, it has been brought to my attention by constituents in New Jersey that the FDA-required med guides are in many instances not distributed when antidepressant medications are dispensed, even though such a distribution is required under the regulations introduced by the FDA, by your agency. In examining this issue, I contacted the FDA representative from the National Association of Chain Drug Stores, the National Community Pharmacists Association, the New Jersey Pharmacists Association, the New Jersey State Board of Pharmacy, and four different drug manufacturers of these products, of antidepressant medications.

In fact, I have two letters that I sent to Dr. von Eshenbach and the two responses that I received from the FDA. Mr. Chairman, I would ask unanimous consent to submit them for the record in this hearing. It has appeared to me throughout this investigation that a significant breakdown is occurring between the FDA and the State regulatory authorities, a breakdown that is depriving parents of children for whom antidepressant medications are prescribed, that their ability to make these fully informed decisions, to have all the information they really need. And med guides are so important because it gives us information in English that normal people can understand.

For example, it is impossible to determine with certainty that the med guides are in fact being distributed with the prescribed antidepressant medications because regulatory authorities at the Federal and State levels are not enforcing the FDA's Stated protocol on medication guides. I am going to just read the portion of the statute that is relevant here, and I quote,

> Each authorized dispenser of a prescription drug product for which a medication guide is required under this part shall, when the product is dispensed to a patient or to a patient's agent, provide a medication guide directly to each patient or to the patient's agent unless an exemption applies under 208.26.

Did the FDA issue this regulation?

Dr. GALSON. Yes.

Mr. FERGUSON. Yes. Thank you. Can you or anybody tell me with certainty that medication guides are being distributed to patients and parents when they ought to be?

Dr. GALSON. Right. I know you are in a hurry. I will be quick.

We have invested a huge amount of time in determining what should be in these medication guides. Every word is looked at very, very carefully because we want these messages to get to patients. So let me make it easier for you and tell you that we share your concern and we are not denying this. We know that in many cases, these medications are not being given out. The challenge, like so many things at FDA, is what is the best thing to do about it. They are required to be given out. On the other hand, we don't regulate the practice——

Mr. FERGUSON. Right, and we are going to get to that right now.

Dr. GALSON. Yes.

Mr. FERGUSON. I appreciate your——

Dr. GALSON. So it is really our interaction with the States and the pharmacy organization.

Mr. FERGUSON. That is exactly right. In my investigation, I also contacted the New Jersey State Board of Pharmacy, and I got this response from Joann Boyer, who is the board's executive director in New Jersey, and I quote,

> The board does have the authority to enforce the Federal regulation regarding the distribution of these guides. An overview of this Federal regulation will be included in the Board of Pharmacy newsletter with a statement addressing the need to be compliant and the fact that our inspectors will be including this item in their normal inspection routines. I will provide the inspectors with all necessary information regarding medication guidelines and instruct them to ensure compliance when they perform their inspections in our retail pharmacies. Those pharmacies identified as being noncompliant will be brought to the board's attention for review and action, which may include financial penalties.

Before my inquiries, States like New Jersey were not using their authority to monitor pharmacists and their distribution of medication guides. Does the FDA have the authority to contact and instruct State board of pharmacy to follow New Jersey's example?

Dr. GALSON. We certainly don't need any special authority to contact the board of pharmacy and encourage them to action. What we have heard from some of the people that we have contacted is that they consider the regulations that we have onerous, that there is a lot of paper, that they don't have the capacity to store all the paper that is required to be given out, and that there are some real logistic issues.

Mr. FERGUSON. Right.

Dr. GALSON. And it is because of this that we have organized and announced a public meeting coming up this spring so we can get the views of all the constituents involved with pharmacies and States, hopefully the patients.

Mr. FERGUSON. That is where I am going next.

Dr. GALSON. They will come with suggestions——

Mr. FERGUSON. We didn't even coordinate this, but that is where I am going next.

Dr. GALSON. Absolutely, yes. We agree this is a problem.

Mr. FERGUSON. I would urge you to use the authority that you say you don't even need, I would urge you to take those actions to contact State boards of pharmacy because there are actions that they could be taking to make sure that parents and patients get these very important information.

Moving on, I have heard from pharmacists in our district and elsewhere that they encounter problems getting the med guides, as you were just saying, from manufacturers and storing the adequate numbers of the med guides in their stores. Shelf space can become an issue. Under the FDA's rule, medication guides must be generated by manufacturers, then sent to the pharmacists, in most instances via a wholesaler and then given to the patient when the drug is dispensed.

Is the FDA monitoring whether manufacturers are actively providing these med guides to pharmacists so they can dispense them to patients? Is that something FDA does?

Dr. GALSON. We certainly could do that. I would have to get back to you. I don't know for sure whether there have been any compliance or inspectional kind of activities specifically focused on that.

Mr. FERGUSON. If it not going on, I would urge the FDA to take that step. That is another potential breakdown, and in some cases I am sure has been a breakdown in the system. Does the agency also monitor whether manufacturers of generic versions of brand name drugs are distributing these as well?

Dr. GALSON. They are required to give out the same forms as the brand names.

Mr. FERGUSON. OK, so they would be included in this oversight as well? In our investigation, the National Association of Chain Drugstores told me that they delivered a proposal to the FDA 2 years ago, asking if they could distribute med guides electronically, thereby greatly simplifying the lengthy and unreliable distribution chain. Can you tell me if the agency will allow pharmacists to print these electronically, just sort of print them off the computer rather than having to store reams and reams of paper in their pharmacy?

Dr. GALSON. Yes, this is one of the issues that we are going to take comment on and talk about at this public meeting. I am not certain whether the electronic provision of an identical medication guide to the one that we require companies to put out, I suspect there is no problem with that. The problem is that the format sometimes changes. It is different, and we have to look at those issues.

Mr. FERGUSON. My time is almost up. I understand in my letter from the FDA that you will be holding a public meeting soon to discuss the distribution of medication guides. I am delighted. That is a very important part of the process. I am pleased the FDA has taken that important step.

My last question. In the last week, the FDA has drafted many changes to the med guide for antidepressants, and I have copies of each of the two. Most strikingly, the title of these med guides was changed. The previous one said "Medication Guide about Using Antidepressants in Children and Teenagers." That title has changed, and I would like to submit both of these for the record under unanimous consent, Mr. Chairman. It was changed to "Medication Guide: Antidepressant Medicines, Depression, and Other Serious Mental Illnesses, and Suicidal Thoughts or Actions." Just seems to me that the old version of the medication guide was more thorough and sort of concentrated exclusively on the potential adverse reactions that could occur when taking antidepressants. The new version seems to sort of delve into a whole discussion on depression. Can you tell me why? Do you have any idea why these changes were made in that way?

Dr. GALSON. Yes, I have a very good idea, and it is not easy to explain. If you could give me just a few minutes to do it. This has been one of the most contentious and difficult areas of drug regulation over the past few years in FDA but not atypical in that new information has been developed about potential risks related to these products since they have been on the market, and those are the risks that are discussed in the med guide with suicidality.

Now, we have taken steps going back a number of years to add information to the labels and to the med guides, making sure that patients and physicians are aware of this new information and what it may mean to patients. And what we have heard is some people think that this is great. Other people think it is bad.

The psychiatric community, the American Psychiatric Association has been very, very angry at the FDA because they think that telling people about these risks is dissuading people who really need these drugs for depression from taking them and therefore contributing to the number of people that are expressing suicidal activity. And this is, of course, something that worries us a lot.

What we try to achieve in our communications products is to balance benefit and risk, which is what is absolutely critical in explaining the risks and the benefits of drugs so that people can make the decisions. So what we have attempted to do with these latest changes in the med guide is not to excessively focus on the risk but also talk about the balance of what these drugs are for, the risks obviously of feeling suicidal, and to make sure that people understand.

And I know that it is a more complex task, but this isn't an easy goal to communicate. We are working. We continue to work with experts on how to communicate with patients and with physicians, and we hope to continue to improve the messages that we are getting across, the points we want to.

Mr. PALLONE. Thank you. The gentleman from Texas, Mr. Green.

Mr. GREEN. Dr. Galson, thank you for being here and listening to all our opening statements before we could actually ask questions.

It is correct that the FDA currently does not have the authority to grant conditional approval for a new drug application. Is that correct?

Dr. GALSON. Yes.

Mr. GREEN. Can you comment on how the extension of your authority to implement a conditional approval process would offer the FDA additional tools to ensure that drug's safety.

Dr. GALSON. Well, that is something that would have to come from you all from Congress to do that. We are implementing a new pilot program, in the center to look back at drugs a year or 18 months after they are approved to see whether new information that has been developed about them changes the way that we balance benefit and risk and may require us to communicate about changes.

Mr. GREEN. So would this stand in the place of a post-market study, or would it just be implemented a second way——

Dr. GALSON. What this pilot project does is it takes the information that is available from the reports that have been submitted by companies from adverse event reports from any information that has been developed in literature, and it has us do an additional benefit/risk assessment to see whether there has been any change and to see whether there are changes that are required and how we communicate. If there is a post-marketing study that has to happen, it wouldn't influence that one way or another.

Mr. GREEN. OK, in your testimony, you indicated that the responsibility for correcting many of the organizational problems has fallen on you and your position. Can you expand on your efforts to focus on the drug safety within the center, particularly what protections as the FDA put in place to ensure that any analysis of post-market data by the Office of Drug Safety is accepted and acted upon in a timely manner? Is there a process going on now?

Dr. GALSON. Yes, there is a process going on now, but as you have heard before, there is a challenge to making sure that the decisions that we come out with at the end of the day reflect the best possible input that we receive from people across the center. And what I have heard is that some people in the process sometimes feel undervalued. And my goal is to make sure that that doesn't happen, that we improve that situation, and that the people from all the different perspectives in the center have those perspectives considered. If there is a disagreement, it comes to light so that we can make sure that the more senior people are the people that have to make those decisions, can weigh the evidence on each side and come out with the right decision.

Mr. GREEN. I think from our hearings in the Oversight and Investigations Subcommittee, that is what we are hearing, that there has been a discrepancy, and some of the FDA employees feel like that their statements or status wasn't considered. So I appreciate that.

Let me ask you a specific issue. I am concerned about the safety of signing both the approval process and the post-market surveillance. On the approval side, there is an issue that has come up about safety issues and particularly surrounding RHLF, recombine human lacto-ferin, which has been widely studied for treatment of serious illnesses, including cancer. On the drug safety side, I think that is on the drug side, but I also understand there is a potential for using that as a food additive. And I have some concerns because the food additives are not as rigidly controlled as a pharmaceutical. Can you speak to that issue?

Dr. GALSON. Well, in general—and I don't want to refer to a specific product that is under review—but in general, of course, we don't want drugs to be put in food. And that would concern me a lot. This particular product is a natural product and, as you may recall a number of weeks ago, that the deputy commissioner, Dr. Woodcock, came and testified to you about follow on protein products.

We have to make sure that if there are products entering the marketplace, they get the appropriate types of medical and other testing that are necessary to make sure that we understand well what the impacts are going to be. This sounds like it is a very complex regulatory matter between the food side and the drug side, and we will have to have our legal experts look into that and follow through on it.

Mr. GREEN. But the concern is that using it as a food additive, the regulation and the oversight is much less as making that an actually prescription drug.

Dr. GALSON. Yes. Well, we have to follow our procedures, but just in general, as I said, the idea of a drug being in the food supply doesn't strike me as a great idea.

Mr. GREEN. I agree, and that is my concern. Thank you, Mr. Chairman. I yield back my 6 seconds.

Mr. PALLONE. Thank you, and we have the other gentleman from Texas, Mr. Burgess.

Mr. BURGESS. Great, I will take the extra 6 seconds. Dr. Galson, Dr. Crosse, thank you both for being here with us. Dr. Galson, let me ask you, you mentioned in your testimony the importance about

communicating and drug safety and the emerging data on drug safety. Do you get an annual report from a manufacturer every year on the anniversary date of introducing a new product?

Dr. GALSON. Yes, we do.

Mr. BURGESS. So we consider that post-marketing information?

Dr. GALSON. We get a huge amount of post-marketing information.

Mr. BURGESS. But that report on the anniversary date, would that be fair to call that post-marketing information?

Dr. GALSON. Of course.

Mr. BURGESS. So how do you utilize that?

Dr. GALSON. Well, we look at those reports. There is a specific requirement that companies let us know about any serious and unexpected adverse events. And those are the ones that we spend the most time looking at very carefully to make sure that what we aren't seeing is a new emerging kind of risk with the product that we wouldn't see before.

So we look at those. We combine it with almost half a million adverse events reports that we get that come into our spontaneous reporting system, separately from that. And we have safety evaluators look at those data and then meet with other staff if there is a concern that is developing.

Mr. BURGESS. So you would regard this information as helpful?

Dr. GALSON. Yes.

Mr. BURGESS. And you have developed the computer algorithms and protocols to help you sift through all that voluminous information?

Dr. GALSON. We need to do a lot more in that regard, and we are moving forward but it is—yes.

Mr. BURGESS. Let us come back to that thought if we have time, but there is also a lot of information that is just out there in the—we might call open source information that is not necessarily the purview of the FDA or even necessarily the—well, we could reference the CMS database, and I am sure NIH has their own databases and their private databases. Do you peruse those sources for information about products, particularly when something has come to your attention?

Dr. GALSON. We look at any available data. I do want to emphasize though that the number of staff that we have been able to devote to this activity traditionally has been limited by our resources, and that is why we have been working through the user fee program with Members of Congress to beef up in particular that part of our operations so——

Mr. BURGESS. Since you brought that up, so how many FTEs do you devote to that? Can you tell us?

Dr. GALSON. Well, it is difficult to say but——

Mr. BURGESS. Perhaps you can provide it after the fact—the number of people who are actively working on that and in an ideal perfect world what that number would be so this committee could perhaps deal with that——

Dr. GALSON. We will get it to you.

Mr. BURGESS. The stuff that is it the open source, do you ever go out and purchase information from private sources?

Dr. GALSON. Yes, we do.

Mr. BURGESS. And is that important?

Dr. GALSON. Extremely important and will be more important in the future.

Mr. BURGESS. And does funding play a role there? Is price important? Is price a benefit for purchase of that private source information?

Dr. GALSON. Price has been important, so that is another way that I am looking forward to more progress.

Mr. BURGESS. Could you possibly again provide us with some actual data on the specifics of what we are talking about so we perhaps could make informed decisions?

Dr. GALSON. Yes.

Mr. BURGESS. And I know in the past, you brought up the question of tension. The folks that do the pre-market and the post-market testing and the tension that exists between them. Is any of this—and I worked in offices. I am well aware of the front office/back office tension that is going to occur. But is any of the tension related to any perceived financial impetus that is placed on either hastening the approval or strengthening the post-market surveillance? Does that enter into the equation at all? Is that something this committee needs to be concerned about?

Dr. GALSON. Well, I haven't seen any evidence——

Mr. BURGESS. Well, let me change the context a little bit because it keeps coming up, and I think that it is a good idea. And I think it is something that we should continue to do, but this concept keeps coming up. It is fair to ask the question is this a problem? Is this entering into the tension equation that you referenced? And if so, could you help us quantify it? And could you help us by providing areas where—if that is an issue, and I don't know that it is—but if it is, how can it be mitigated? How can it be qualified?

Dr. GALSON. Yes, I may have misunderstood you. You mean the disparity in funding issue, but that is a factor if that is what you mean. I am not sure what you mean by financial.

Mr. BURGESS. The theme keeps recurring that there is a problem with how the FDA does its work because of undue influences that are placed on it by outside industry because of the funding mechanism, and I don't know. Is that the situation or not?

Dr. GALSON. I wanted to make sure I understood what you were saying.

Mr. BURGESS. Is that a source of the tension that you alluded to?

Dr. GALSON. I don't think so. There are 2,300 people in the drug center, and no matter which office they are in, they are very, very dedicated to doing the right thing for public health regardless of where their source of funding is. Individual drug reviewers don't know if their salary is coming from user fees or from appropriations. I haven't seen any evidence that that is a factor.

Mr. BURGESS. Thank you. That is a very direct answer, and I appreciate that. Mr. Chairman, I will yield back.

Mr. PALLONE. Thank you. Ms. Eshoo.

Ms. ESHOO. Thank you, Mr. Chairman, and thank you, Drs. Galson and Crosse for your testimony and the answers that you have given to the questions that have been posed by my colleagues. I want to make a couple of comments before I ask my questions. Number 1, the whole issue of advertising, of drugs. I can't help but

think it is kind of in the middle of this. I mean the heavier something is marketed, the more pressure there is to buy, and obviously, this pipeline to examine and for efficacy and then the pressure that I think justifiably is brought on the Congress and the agency for post-market surveillance.

For the life of me, I really don't know what good advertising has done except for, I mean for corporate reasons to market. And I can't help but think that we should revisit this. We should take a look at this and not only examine, in my view, the genesis but all the issues that surround it. To see someone skipping through a meadow, and the tagline being buy such and such a product. I remember my mother used to say, "what is it that they are advertising here?" So I think that we should take a look at that.

It is curious to me of the whole issue of reimportation being raised by Members here. I have always thought that it was a very important issue, and there is the bastardization of drugs by others and the attempt to bring them into the country. But I also think it is a political curiosity about what the Congress did in the name of trying to save money to bring other drugs into the country. I never thought that was a good policy. I didn't support it. I don't support it now, and I think that we have our hands full because there is more and more coming into the country. And we have to take a look at what to do with it.

Now, my questions. In your testimony, Dr. Crosse, you found that FDA's access to post-market clinical trial and observational data is limited by both resources and by authority. This is a softball issue, but do you think that the FDA should have such an authority?

Ms. CROSSE. Yes, we do. We have recommended to Congress to do that.

Ms. ESHOO. Right. Now, would the administration's PDUFA for a proposal include this authority, and specifically what types of post-market observational and clinical studies will FDA be permitted to exercise under the administration's plan?

Dr. GALSON. Right, in our PDUFA proposal and in the legislation that is on the Hill, we will get important new sources of resources——

Ms. ESHOO. Does the Waxman-Markey legislation match what the administration has proposed?

Dr. GALSON. I don't believe it does.

Ms. ESHOO. It doesn't?

Dr. GALSON. Yes, I am not an expert.

Ms. ESHOO. OK. One, I think, is stronger than the other?

Dr. GALSON. I believe so, yes.

Ms. ESHOO. OK, so it is Waxman-Markey that is the stronger of the two. I think we should know that. I mean in my view it is. Do you agree?

Dr. GALSON. It depends which provision specifically you are talking about here.

Ms. ESHOO. Well, overall, is it weaker or is it stronger?

Dr. GALSON. I don't like that characterization.

Ms. ESHOO. OK, I think we know what the answer is here. All right. Now, thank you. I want to go to something that I feel strongly about, and that is health information technology. Your testi-

mony, Dr. Galson, indicates that an additional $4 million is adequate to upgrade FDA's current drug review system. Is it really? I mean what is an additional $4 million going to buy?

And how long will it take to go to full implementation? This is about, my colleagues, I think this is about expeditious review. I mean I don't know. Someone is sitting in a back room and going through this sheet by sheet. Or is it all part of a technology system? First of all, what is the $4 million going to buy? Is it really enough, and how soon does that get the agency to full implementation?

Dr. GALSON. We are in the middle of a very rapid transformation from a paper environment to—there are some areas, depending on what you are talking about, where the technology is there.

Ms. ESHOO. Help us. We want to help you accomplish this.

So what is the $4 million going to buy?

Dr. GALSON. The $4 million is helping us move from a paper system to an electronic system.

Ms. ESHOO. How much of the system is still paper, using percentages?

Dr. GALSON. A lot of it is still paper.

Ms. ESHOO. But give me—come on.

Dr. GALSON. I think we are getting about half of all our applications in by paper, but again that is from the pharmaceutical industry. We need to get there faster.

Ms. ESHOO. I think we need to revisit this, and I think that you are tremendously low balling the amount of money that needs to be invested in this. We should really take a look at it. You tell us what you need to move to full implementation and over what period of time. $4 million, my sense is, represents snail's pace.

Dr. GALSON. We will be happy to get you there.

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

Mr. PALLONE. Thank you. Mr. Murphy.

Mr. MURPHY. Thank you, Mr. Chairman. Doctor and Doctor, I don't know if you heard some of my opening comments about my concerns about the breadth of the kind of warnings and comments made when FDA approves a product. That currently it is one that focuses, I think, a lot of the other reactions and things, but part of my concern as a psychologist, at least when it comes to psychiatric medications, particularly pediatric ones, that I am concerned that 75 percent of drugs are prescribed by non-psychiatrists and that oftentimes there may not be coordination with other people providing consultation with the family and therapy, et cetera. What kind of actions does and can the FDA do to make sure that the proper use of the medications and not just prescribing them is part of the plan?

Dr. GALSON. Right. We, as you know, we don't regulate the practice of medicine. So what goes on in the prescribing room and all sorts of other questions having to do with the way physicians work is not under our purview. But what we do do and what we are very, very committed in is making sure that physicians have the best possible information as quickly as possible when we develop new recommendations or new views about safety and efficacy, the benefit and risk of products.

And we see our role here in making sure that the information accompanying products, the information that is available to the public, is as accurate as possible. We also work with professional organizations, the people who provide different, some specialty organizations. When there are issues, we bring them in. We talk to them, so that is the way that we work with the medical community, but we don't actually have regulatory authority over that operation.

Mr. MURPHY. Dr. Crosse, do you have some comments on that?

Ms. CROSSE. No, we are well aware that this is an issue for the FDA and that many of the problems that have arisen with drugs and some of the post-marketing safety concerns that have arisen have been in instances where medications have been prescribed that are not in accordance with the label indications or for populations for whom they are not indicated. And FDA, in a number of instances, has taken additional steps to try to add warnings to the labels of those drugs to try to put out information to the public and to try to put on some other kinds of controls on who can prescribe these medications. But it remains a problem of great concern.

Mr. MURPHY. Certainly, Dr. Crosse, you are involved with some of the labels and some of the information that goes to physicians on things even though you can't regulate them and tell them who has to do it. When it comes to some of these psychotropic medications, however, what kind of commentary goes into the warnings, et cetera, with regard to, I guess, the pool of knowledge someone should have or that medications should be used in conjunction with other types of treatment.

Dr. GALSON. Well, we have a team of people who are experts and psychiatrists who look specifically at the labeling and the information that we provide to the public about that kind of medication, as we do oncologists for cancer drugs. And we get together, and for a new drug, we look at the information that is available from the clinical trials.

And we determine the best way to communicate about that, having to do with the dose, having to do with contraindications, other types of warnings or precautions, concomitant diseases that may affect the use of the drug. And we endeavor to make sure that all that information is put together in the drug label, and if there are special ways that that has to be communicated, we will get together and discuss that as well.

Mr. MURPHY. But is it done, again the psychotropic medications, where it is described that the medication—the volumes of research indicate it should be done, provided, in the context of a sort of structurally trained psychotherapy and monitoring these cases, No. 1. The second issue is that in many cases, I don't know if these drugs are really evaluated on a pediatric population.

What is done to communicate those issues of the full spectrum of treatment under which these medications seem to work best?

Dr. GALSON. Our authority doesn't, in most cases, extend to some of the things that you are mentioning. When we do think that there is a drug that has such severe risks that we think that only a physician with a certain kind of training should give it. Or there is a drug, for example, that has risks that we think it should only be administered in a hospital, we can require that.

Mr. MURPHY. Well, I am not saying just in terms of who prescribed it, but also other components of therapy that go with that. Many medications may have other side effects. Take insulin for diabetics. It is not enough just to say here is the insulin, but it should be used in accordance with a strict dietary and exercise information.

Dr. GALSON. We can put that information in our labels, and we do all the time.

Mr. MURPHY. I am not sure that is done adequately when it comes to psychiatric medications, especially when it comes to recognizing a lot of these medications have not really run through proper trials on a pediatric population.

Dr. GALSON. Right. We have under our authorities to require and to urge that studies be done in pediatric populations. We have succeeded in having more of the studies looked at for younger age groups, but there is no question this is a challenge.

Mr. MURPHY. I would hope, Mr. Chairman, as we pursue this because our culture is becoming so much giving kids drugs, and it is amazing how many youth are given drugs for psychiatric reasons to quiet them down, to stabilize them. And the almost explosion of diagnosing these things. I really hope this is an area that you continue to investigate. Thank you very much.

Mr. PALLONE. I appreciate your comments. I agree with you. I recognize the gentleman from Massachusetts, Mr. Markey.

Mr. MARKEY. Thank you, Mr. Chairman, and again I appreciate your giving me this opportunity. Mr. Galson, Mr. Waxman and I have introduced the House counterpart to the Kennedy-Enzi drug safety legislation, which includes many of the recommendations of the Institute of Medicine and GAO. And we are hopeful that it will be included as part of PDUFA reauthorization on the House side. So Dr. Galson, if I may, my wife is a doctor. So I apologize for calling you mister.

Dr. GALSON. I am a doctor.

Mr. MARKEY. Doctor, yes, I apologize. Let me begin with you. In response to Chairman Pallone's questions about clinical trials, you stated that there has been tremendous improvement in registration of clinical trials. However, companies aren't in 100 percent compliance with registration of required trials. Is that correct?

Dr. GALSON. I am not sure that is exactly what—you are quoting my response from just a few minutes ago?

Mr. MARKEY. Yes, they are not in 100 percent compliance.

Dr. GALSON. I would have to look specifically at the rules. What I believe I was trying to convey is that not all the detailed information that some people think should be put on public databases, going down to patient-level data, is on there. I am not aware of compliance issues.

Mr. MARKEY. OK, would you agree that if registration is not mandatory and the FDA does not have any enforcement mechanisms to require registration, that we will never get 100 percent compliance?

Dr. GALSON. I don't know really and wouldn't want to speculate.

Mr. MARKEY. And I appreciate that.

Dr. GALSON. Yes.

Mr. MARKEY. If we are trying to ensure that we know about all of the trials that have been conducted on a product after phase one and eliminate the problem of selective disclosure of trial results, which can give the public a distorted view of the risk of benefits of the drug getting most of the trials doesn't really fix the problem because the trials the companies are registering may be the most important for the public to know about. By only selecting the answers that you want to give, the public might be denied information that could be useful, or the physicians could be denied the information. Do you agree with that?

Dr. GALSON. I agree that it is very, very important when there is a marketed product, if there is a clinical trial that is done that is relevant to patient care and drug safety, that it is important that the information that could have an impact on whether patients and physicians want to use a drug, that that be available.

Mr. MARKEY. OK. And, Dr. Galson, some people have raised the concern that emphasizing post-market safety could slow down the approval process. However, it would seem to me that if FDA is confident in its ability to detect and manage problems after approval, then the FDA should actually be able to approve the drugs faster even if there are some lingering questions about the safety preapproval because there will be a strong system to monitor and invest those issues, if necessary, after the drug is on the market.

Do you agree that having a stronger post-market safety system, a safety net if you will, is important to giving the FDA the confidence that they don't have to catch everything pre-approval because the approval is not the last chance to address the safety issues.

Dr. GALSON. That is a complex, multi-part question. Let me just say starting that it is not possible to catch everything with the current state of knowledge. If we want new products for patients who need them, we are going to sometimes find out things after approval that we didn't know when the drugs were approved.

Mr. MARKEY. So the point I am making is don't you think a stronger post-market safety system would give people more confidence?

Dr. GALSON. Yes, I am a very strong supporter of a stronger post-market safety system.

Mr. MARKEY. OK, Dr. Crosse, in your testimony, you described some major gaps that currently exists in the FDA's post-market safety net system. In his statement, Dr. Galson testified that the FDA's PDUFA proposals will transform the drug safety system at FDA. Do you believe that additional resources for post-market safety without additional authority to require post-market studies and changes is enough to transform the post-market drug safety program in FDA?

Ms. CROSSE. We believe that additional authority is warranted for FDA to give them all the tools that they need to be able to effectively oversee this process.

Mr. MARKEY. How does FDA's current lack of authority to require post-market studies affect the FDA's ability to assess safety problems after a drug is on the market?

Ms. CROSSE. I think it complicates and slows the availability of information that is needed to be able to fully understand certain

types of problems. Absent certain types of information, the agency often cannot make a determination quickly or possibly even at all about what kind of action ought to be taken.

Mr. MARKEY. I thank you. I think of it as a trainer for tightrope walkers. Before the walker steps off the platform, the FDA is in a strong position to make sure the walker will succeed by requiring a harness, if necessary. But once the drug is approved and the walker leaves the platform, the FDA can do little to require protections if companies don't want to accept them.

Knowing this, the FDA is unlikely to let products go if felt a little wobbly. However, if the FDA had a strong safety net in place to catch problems and prevent a major crash, the FDA is more likely to feel comfortable in getting products to patients who need them. That is what the Waxman-Markey safety bill would do. It would create a strong but flexible drug safety net, and it is something that, I believe, at the end of the day is actually essential to having a good drug approval system. I thank the chairman for allowing me that little extra time.

Mr. PALLONE. Thank you, Mr. Markey. That concludes our questions, and thank you both for being here today. I thought it was a very good questions-and-answers series. Let me just say though that we are going to take a break before the second panel goes in. We have 11 minutes left on one vote, and then there will be three 5-minute votes after that. So figure about half an hour we will be back and start with the second panel. But we are now in recess. Thank you.

[Recess.]

Mr. PALLONE. The subcommittee hearing will reconvene, and I will ask the panelists to come forward and sit down. Welcome to all of you. Let me introduce each of you actually. We have a pretty large panel here today.

We will start on my left with someone from New Jersey, Lisa Van Syckel, who is from Flemington, New Jersey. We are going to have a video that she has brought us. And then we have Dr. Ellen Sigal, who is chairperson and founder of the Friends of Cancer Research. And Dr. Susan Ellenberg from the University of Pennsylvania School of Medicine. She is speaking at the request for the Coalition for a Stronger FDA. Dr. Caroline Loew, who is senior vice-president for scientific and regulatory affairs of the Pharmaceutical Research and Manufacturers of America. Diane Thompson, who is vice-president for Public Policy and Communications at the Elizabeth Glaser Pediatric AIDS Foundation. She is speaking on behalf of the Alliance for Drug Safety and Access. John Theriault, chief security officer and vice president, global security at Pfizer. Dr. Sharon Levine, associate executive director for the Permanente Medical Group, speaking on behalf of the Kaiser Permanente Medical Care Program. And Dr. John Powers, who is assistant professor of medicine at George Washington University School of Medicine, and I guess also at the University of Maryland School of Medicine. So thank you all for being here today. We are going to start with Ms. Van Syckel, and does the video go first, or how does that work? We will do the video first? Now, we were going to try to put it on the big screen, but it didn't work. So we are using the TV. Thank you.

[Video shown.]

Mr. PALLONE. First of all, let me thank you for being here and for bringing us the video and relating your own story of your daughter. I know it has got to be tough, but we really appreciate your being here.

STATEMENT OF LISA VAN SYCKEL, FLEMINGTON, NJ

Ms. VAN SYCKEL. Yes, it is very tough, and I just want to make sure that no family ever has to endure what our family endured. The FDA and pharmaceutical industry continues to downplay the risks of antidepressants in children. They have gone from causal low to increased risk and to most recently the Johns study, saying that the benefits of antidepressants outweigh the risks.

When we hear about increased suicide within the media, they think that it is something that is very quiet. And that is why I thought it was important to come and play the tape so Congress can actually see it for themselves, hear about it, because it is a violent suicide. It is not something quiet, and I think it is very disturbing for this FDA to allow the pharmaceutical industry to negotiate the labels that are placed on antidepressant medications.

They should never be allowed to negotiate the lives of our children, and I think that is what the very important issue here is. And, Mr. Chairman, we have another serious concern, especially in the State of New Jersey where infants are being given antidepressant medications, not only antidepressants but antipsychotics to medicate children as young as infants, 12 months. And we need to ask why.

So with the FDA and their failure to provide the medication guides, which is an issue I have been speaking with Mr. Ferguson, it is quite clear that the FDA is incapable of doing their job and notifying the public of severe side effects. And I am begging you, as parents from the State of New Jersey, from district 6 and district 7, because I represent all of New Jersey, we need an independent office of drug safety.

We need better control of direct consumer marketing, and we need a better med watch program. I want to give you an example. My brother had a severe condition and was critical, and a nurse had stated to me—I said "well, what about the side effects." And it was the particular drug Zocor. And she says you can actually get the side effects from the television, from the commercial. And I said to the nurse you are telling me, as a caregiver, that I should look to the television, to a commercial for side effects. That was ridiculous, and I said I think you are saying that to the wrong person.

So I am really concerned as to the direct consumer marketing. I realize they have a right to free speech, but medical professionals should not be telling patients to watch it on TV.

[The prepared statement of Ms. Van Syckel follows:]

STATEMENT OF LISA VAN SYCKEL

Mr. Chairman, members of the committee, thank you very much for inviting me to testify at today's important hearing.

I would like you to hear how corporate greed, our woefully inadequate mental health system and over-reliance on pharma-psychiatry, and the little pink pill, Paxil, have forever altered the life of my most precious gift from God, my daughter Michelle.

Michelle was raised in a loving, stable home in the small town of Dunellen where she participated in many community events and was proud to be a girl scout.

In 1995 American Standard transferred my husband to their European Division in Brussels, Belgium.

Michelle, who had always been an honor roll student, attended St. John's International School in Waterloo. Michelle traveled and explored many European countries. She became fluent in the French language.

Our family returned to the United States in the summer of 1999. Our life, as we once knew it, would change dramatically. Michelle began complaining of ill health and missed her friends in Belgium. She was also upset over the declining health of her grandmother.

In April 2000 Michelle continued to complain of ill health, she was losing weight and had stopped eating. She was admitted to Somerset (New Jersey) Medical Center's eating disorder unit, where she was diagnosed with depression and anorexia nervosa and was prescribed the antidepressant Zoloft. Within hours of digesting Zoloft, she reported to hospital staff that she had the urge to hurt and cut herself and two days later, again reported she was uncomfortable taking the medication. Her complaints were dismissed. Several weeks later, Zoloft was discontinued due to dramatic orthostatic changes and bradycardia. (very slow heart beat). Michelle became very hyperactive and was diagnosed with a personality disorder. No one apprised me of what was happening to her. She was fourteen; I should have been informed.

In June 2000 Michelle was placed on Paxil. Within a few weeks she began to self-mutilate with knives, razors and broken plastic CD cases. She became verbally abusive and was displaying extreme oppositional behavior, along with severe insomnia, diarrhea, chest pain, weak muscles, and on a few occasions vomited blood and had rectal bleeding.

In August 2000 the Paxil was increased to 40 mg along with a diagnosis of major depressive disorder with psychotic features.

In September Michelle's self mutilating behavior was increasing. During one episode, she had inflicted over 23 wounds and cut the word "die" onto her abdomen. She became violent and suicidal and was hospitalized because she was deemed to be a danger to herself and others. Her Paxil was reduced from 40 to 20 mg and Depakote was prescribed.

On October 6, 2000 my daughter Michelle attempted suicide and became extremely violent. She assaulted her brother as he was desperately trying to keep her from killing herself. He was just 4 days shy of his 12th birthday. She then viciously attacked three police officers and managed to escape from her handcuffs twice. She was kicking, spitting and screaming obscenities. She even attempted to kick out the rear window of the patrol car. When they arrived at the hospital, it took five men to place her in leather humane restraints. The next day Michelle awoke dystonic and unaware of her surroundings. Again, she became violent and had to be restrained.

Michelle was transferred to UMDNJ Behavioral Health. Paxil was discontinued, but she was then prescribed Celexa and Risperdal (what I didn't know then, but have since learned, was that Michelle was placed in a clinical trial of these drugs without my knowledge or consent). Within 36 hours, Michelle again became violent and self mutilated. She was injected with Thorazine for her out-of-control behavior.

Approximately two weeks later, she was released from UMDNJ with a 3-day supply of medication (what I know now and didn't know then, was that this was a very dangerous thing to do). In an abrupt withdrawal, Michelle again became violent and threatened to kill me. She thought I was the devil and told me I was evil.

In April 2001 Michelle was removed from all psychotropic medication. Recovery was a long, tedious process. Everything Michelle endured while on the drugs was suffered through the withdrawal process.

Michelle's Paxil-induced psychosis, self-mutilation, violent, and suicidal behavior are gone now. What remains upsetting is that the physical scars of her self mutilation will be with her forever.

Michelle's beautiful smile and sweet disposition were returned. Michelle never had violent and suicidal behavior prior to taking antidepressants, nor displayed this behavior after recovering from withdrawal.

I believe, without question, drug companies and their apologists are putting a great deal of pressure on the FDA. Despite all of the controversy and exposed failures surrounding the FDA in the last few years, it appears that the FDA simply cannot muster the guts to act without industry influence. Absent this influence, there would be no reason why the FDA wouldn't insist on label warnings for all ages on anti-depressants. No doubt drug companies are a formidable force, but the FDA

must remember whose interests it is supposed to protect. If it does not, the representatives of the people, Congress, will have to step in and do it for them.

I would like to show you about a minute and half of a video of Michelle and other families' children who have suffered because the FDA failed to better warn the public about dangerous side effects.

LEGISLATIVE SUGGESTIONS

So that other families are saved from the tragedy and heartbreak that my family and other families in this hearing room have endured, I urge you to approve—as part of the must-pass user fee legislation—the strongest possible FDA drug safety reform legislation.

PDUFA: Break the ties that are distorting the FDA's mission. First, on the extension of the Prescription Drug User Fee Act (PDUFA IV), I know that the FDA needs the resources, and more, that the user fees bring. The user fees need to be continued, and expanded to provide more resources for safety.

But under the current law, the industry's user fee money comes with a huge cost. It comes with detailed requirements to serve the drug industry—and that is a cancer that is eating at the culture and integrity, both real and perceived, of the FDA. If anyone doubts that the user fees are having a corrupting influence on the culture of the FDA, I urge them to read last summer's poll by the Union of Concerned Scientists, to which about 1000 of the FDA's medical scientists responded. Many poured out their frustration at being pressured to approve drugs on which they had serious safety concerns, and a number cited PDUFA as an inherent conflict of interest. A recent study by a group of Harvard researchers has found that drugs approved just in time to meet the PDUFA time goals have many more post-market safety problems than drugs which receive more review time. An earlier study by Harvard Professor Daniel Carpenter pointed out that the FDA's time-to-approve drugs was declining in the years before PDUFA's first passage in 1992; the study found that the FDA staff was being increased through regular appropriations, and that every 100 person increase in staff was resulting in a 3.3 month decline in approval times. I think this study shows that while the FDA does need more resources, it does not need the rigid framework of PDUFA.

This committee is famous for its tough oversight. I am sure that you can make sure that the user fee money is well spent and that the FDA continues to give priority, timely attention to truly life-saving drugs. Therefore, I urge you to break the entangling webs of obligations that come with the user fees and just let the FDA use the fee money to do its job. Congressman Hinchey has previously introduced legislation that would achieve this reform.

Kennedy-Enzi (S. 1082), and Waxman-Markey (H.R. 1561)

The bill the Senate is passing makes important improvements for safety. And in many ways, the bill by Representatives Waxman and Markey is even better, because it

- requires a warning signal for the first 2 years a drug is on the market (an important fact for consumers, since the real test of a drug's safety comes once it is mass marketed and used by the general population);
- requires a review of a drug's safety history after 7 years (important because only about half of a drug's side effects and labeling changes are detected in the first 7 years it is on the market);
- provides much more meaningful civil monetary penalties than the Senate bill;
- protects the public from overuse of particularly dangerous drugs by limiting direct-to-consumer ads for up to three years; the First Amendment does not give the drug companies the right to kill Americans, and moderation of ads on a new drug with serious warning signs of danger should be one of the FDA's tools;
- ensures that the results of all clinical trials (other than phase 1 trials) will be made publicly available in a timely manner.

To save other families from future drug safety disasters, I urge you to take this best opportunity in the next five years to pass this kind of legislation, and I urge that it be made even stronger.

We need a better Adverse Event/MedWatch Reporting system. The Senate bill includes a major new monitoring of huge medical databases to detect quickly problems with drugs. It is said that the problems with Vioxx might have been detected in about 3 months under such a system.

But I believe we also need to educate and involve the American consumer more in reporting adverse events. Today, the average citizen has no idea how or where to report a problem with a drug. I urge you to require all drug ads to prominently display a 1–800 number where problems can be reported. The FDA should also start

using the tools of the Internet and e-mail to, with patients' permission, periodically query people who are taking a new drug whether they notice any adverse reactions. Instead of passively waiting for reports of trouble, a modern FDA should be seeking out the areas of danger.

We need someone responsible and accountable for safety at the FDA. I support a separate Office of Drug Safety in the FDA, one that will be free of the control and overwhelming presence of the Office of New Drugs.

The FDA Commissioner and many others have said that a separate office would be duplicative, expensive, and hold up approvals. If that is a problem, the same goal of accountability for safety could be achieved by giving the head of the Office of Drug Safety the power to call for a safety action (a REMS adjustment in HR 1561). If the head of the Office of New Drugs disagreed, the Commissioner would decide between them, all within a week or so (so that there can be no charge that we are delaying the approval of vital new drugs). There needs to be a locus of safety accountability in the FDA. This proposal, or a wholly separate office, would achieve that goal.

No Conflicts of Interest (COI) in FDA Advisory Committees. The FDA recently announced guidance that makes major improvements in the Advisory Committee (AC) process: no participation in an AC if one has over $50,000 in conflicts, and participation in the AC, but no vote if one has any conflict. I hope you will codify the FDA's action, but go beyond it by requiring the active recruitment of COI-free experts, and prohibiting those with conflicts from sitting with the AC (they can testify, but they should not be part of the camaraderie-building AC process where they can influence outcomes even though they can not vote).

Thank you for your consideration of these legislative ideas. If enacted, you could give the American people the FDA they need and deserve.

Mr. PALLONE. Thank you. And we are going to ask you some questions later, but thank you for being here today. I appreciate it. Dr. Sigal.

STATEMENT OF ELLEN SIGAL, CHAIRPERSON AND FOUNDER, FRIENDS OF CANCER RESEARCH

Ms. SIGAL. Thank you, Mr. Chairman, members of the committee. Thank you for the opportunity to testify today about drug safety. It is an extremely important issue.

My name is Ellen Sigal. I am chair of Friends for Cancer Research. Friends is a coalition of all of the major groups in cancer research. Our mission is the importance of cancer research. We represent patients, scientists, clinicians, cancer center directors, and we care deeply about research.

The issue of drug safety is very personal to me. My own sister died 21 years ago of toxicity of a drug for breast cancer. So I know personally what this means. She left a 4-year-old child. So this is a very important issue to me and to all of us.

My testimony will cover four major points today that are extremely important to the patient community and the science community. Patients needs for life-improving therapies and a crucial pipeline and access to drugs, providing additional resources for FDA—you have heard that before, and you have heard it here again—establishing a systematic routine and easily accessible safety monitoring system, and finally integrating science into the regulatory process, the critical path initiative and the proposed FDA foundation. I also do want to point out that the president of Friends, Molly Mallick, is here today, and I thank her for coming here and supporting us.

Millions of other people have shared my experience and care deeply about this issue of drug safety, just as Ms. Van Syckel and others that you will hear today. So this is a concern that the pa-

tient community cares about deeply. I am going to read a quote from Meryl Wineberg, who is the chair of the National Health Counsel. "Speaking on behalf of 100 million Americans with chronic conditions and disabilities, it is equally important that patients whose quality of life or indeed life itself are not deprived of the medications they need." I did have other testimony for the record from the American Cancer Society and other patient groups.

When the issue of drug safety was surfacing and it was clear there were going to be hearings and legislation about it—we are very research oriented at Friends of Cancer Research, and we convened a group of experts in cancer and outside of cancer, clinicians, scientists, epidemiologists, patients, to look at the issue because we wanted to have an informed position on this. And we wanted to make sure that we looked at the position from a scientific point of view. We are science oriented, and we thought it was important to have clinicians, people that actually treat patients, weighing in on this issue.

Our major recommendations—the White Paper is drug safety and drug efficacy. I would like it to be submitted to the record. Thank you. The paper highlights three major areas: active surveillance, systems of the life cycle of a drug. We don't have all the information up front in preclincal environment. We really find most of it in post-surveillance. Resources for the FDA and training, training for FDA personnel. That is absolutely critical. The integration of science through critical path, and the public/private partnerships. We can't, as much as we need to fund FDA, and we support substantial increased funding, partnerships through this critical path initiative and this hopefully relief from foundation will be critical to it.

We also think that we have to use existing networks, such as the VA, Kaiser, Blue Cross and others. The database and the information they have are critical. I want to read a quote from the recent IOM report. The recent IOM report on drug safety states "to expect a pre-market studies or FDA review of these studies can reveal all the information about the risks and benefits of new drugs that is needed to make optimal treatment decisions with occasion and reasonable delay in approval."

Authority is fine for the FDA. We support additional authorities. We do not support those authorities without the resources crucial to make these informed decisions. FDA is a chronically underfunded agency that is continually assigned more responsibilities without matching resources. It is unreasonable to starve an agency of the resources it needs yet hold it solely accountable for protecting the health of Americans.

One thousand five hundred people a day die of cancer. Four thousand will be diagnosed today. They cannot afford to wait. They need new treatments. Other patients with chronic diseases need treatments too. They deserve better treatments and more informed treatments. They should be safe, and they should be effective.

The pipeline for these new patients is critical. They must be informed and must have choices, and allow them to participate in the process. Patients are crucial to the process. Patient needs are not monolithic, nor do all patients respond the same to a particular

treatment. Only science and evaluation of patients will really make us understand that and why that happens.

In conclusion, we remain extremely supportive of the goal to improve our drug safety system, and we believe that we can best achieve this goal through a science-based approach, taking into full account the voice and perspective of patients. We applaud the committee for holding these hearings, and we welcome further thoughtful policy discussions. Thank you.

[The prepare statement of Ms. Sigal follows:]

STATEMENT OF ELLEN V. SIGAL

Mr. Chairman and distinguished members of the committee, I thank you for the opportunity to discuss the important topics of drug safety and efficacy as the committee begins to take important steps to strengthen FDA as part of the upcoming reauthorization of the Prescription Drug User Fee Act.

My name is Ellen Sigal, and I am the Chair and founder of Friends of Cancer Research. Friends is a non-profit organization that over the past 10 years has pioneered innovative public-private partnerships, organized critical policy forums, educated the public, and brought together key communities to develop collaborative strategies in the field of cancer research. We are a coalition of major cancer groups representing patients, researchers, physicians, and survivors. It is our belief that a science-guided approach will best enable us to improve drug safety and efficacy in this country.

We urge this committee and Congress to pursue a legislative course that provides FDA with the resources it needs to conduct systematic risk assessment across a drug's lifespan while protecting patients' access to needed treatments. Specifically, we believe that any legislative approach to strengthening FDA must give priority consideration to:

- Patient need for life-improving therapies
- Providing additional resources for FDA
- Establishing a systematic, routine and easily accessible safety monitoring system
- Integrating science into the regulatory process through the Critical Path Initiative and the proposed FDA Foundation

We all want the safest possible drugs. But we recognize that no drug is 100 percent safe or 100 percent effective. We also realize that each patient responds differently to medication. Like the patients I speak on behalf of, and many of you in this room today, I have encountered this reality in a very personal way.

Twenty years ago, my own sister died of toxicity associated with a bone marrow transplant to treat metastastic breast cancer. She was 40 years old and left behind a 4-year-old daughter. This was a tragic event that clearly changed my life. While I hope that no one would have to go through such an event themselves or with their loved ones, this was a risk that we knowingly accepted based upon what was best for my sister at the time.

As emotional as my experience was, I recognize that emotions cannot be the guiding force behind decisions about what treatments should and should not be available to patients. We believe that a science-driven approach to drug development and approval will help to ensure that each person receives the treatment that is most likely to be effective and safe for them.

In examining treatment options, all patients must weigh the benefits and risks when determining their own course of treatment. Legislation aimed at strengthening drug safety must take care to preserve patients' access to a wide array of treatment options while not impinging on the development of new treatment options or removing existing options for patients in need—bearing in mind that for many diseases, including many cancers—patients still have few or no treatment options available to them at all.

We are confident that increased funding for FDA and policy that is grounded in science can achieve an optimal balance between protecting patients and expanding treatment options. A benefit-risk approach conducted across a product life cycle—guided by sound and systematic data collection and careful, regular assessment of a drug's safety and efficacy across subpopulations, dosage levels, and other factors—is the cornerstone of drug development and should be the foundation of drug regulation.

In any treatment decision, consideration must be given to the condition the drug is meant to treat as well as to the extent of the patient's disease, its duration and its impact on the patient's functional status and quality of life. Depending on the particular illness, drugs can potentially be designed for and used at a specific point in the continuum of disease from prevention to terminal illness. Patients' needs are not monolithic, nor do all patients respond the same to a particular treatment.

Legislation should acknowledge the great variability across diseases, patient preferences, and individual circumstances and facilitate continued access to a wide array of treatment options accordingly. Indeed, across the board, one need stands paramount for patients—it is the need for more and better options to fight disease and improve disability. We believe that any legislative initiative that limits patient choice and access to treatments in the name of safety would be counterproductive and not achieve the goal of improving patient outcomes.

As this committee considers ways to enhance the FDA's ability to monitor drug safety to help patients make the most informed decisions about their treatment options, it is of the utmost importance that patient needs and voices be at the forefront of discussions and that all decisions pertaining to drug safety be driven by sound scientific data.

Dr. Jerry Yates, National Vice President of Research for the American Cancer Society, describes a scientific foundation for FDA:

"Based on the course of cancer—from prevention to terminal illness—improving the science of safety will help identify the proper balance between risk and benefit for each stage of the disease and assure optimal investments in both cancer research and the care of patients."

This issue, of course, impacts not only the cancer community, but the entire patient community as well. For example, Myrl Weinberg, president of the National Health Council, expresses her community's needs:

"Of course, prescription drug safety is of paramount importance, and—appropriate measures should be taken to ensure the public is not unnecessarily exposed to—potential harm. However, speaking on behalf of 100 million Americans with chronic conditions and disabilities, it is equally important that patients—whose quality of life,—or indeed life itself—are not deprived of the medications they need."

Lauren Roberts, a multiple sclerosis (MS) patient who was directly affected by the temporary removal of Tysabri from the market, described her experience by saying:

"MS progresses on its own timetable, not the FDA's. In the course of 90 days, there will be, on average, 2,160 more people who hear the words, "You have multiple sclerosis." My own MS continues to ravage my body—Tysabri was the first and only therapy that helped me—the small risk from Tysabri pales in comparison to the risks created by not having Tysabri available to us as a choice—As for me, I am willing to take that risk, in exchange for having an improved quality of life, my life, back.[1]

FDA must have the best tools to make these important assessments and effectively communicate with physicians and patients as they together make individual treatment decisions. New policy to expand the authority of FDA alone will not sufficiently strengthen the agency. Simply put, FDA needs more dollars from Congress. This is a chronically under funded agency that is continually assigned more responsibilities without matching resources. It is unreasonable to starve an agency of the resources it needs, yet hold it solely accountable for protecting the health of Americans.

Now, in a time when public perception is declining, user fees are not the best answer. Due to the current budget climate, user fees are a reality, but a strong FDA is an investment in patient and public health. Congress should find the money to invest.

DRUG SAFETY & DRUG EFFICACY: TWO SIDES OF THE SAME COIN

Several months ago, we convened an independent committee of expert academic scientists and clinicians, research advocates, and representatives of the patient community to examine and recommend ways to further strengthen the agency and its product evaluation process.

It is extremely important that the patient voice be heard along with the perspective of expert clinicians experienced in clinical trial design and translational research. The members of this committee are distinguished experts in diseases such as cancer, infectious disease, and diabetes. They are experts in drug development

1 Roberts, Lauren. Multiple Sclerosis Patients v. FDA Over-Caution. Washington Legal Foundation. May 19, 2006

but also have first hand knowledge in patient care and patient needs. This is a vital perspective that cannot be excluded from the drug safety debate.

I would like to thank Dr. Robert Young, president of the Fox Chase Cancer Center in Philadelphia and chairman of the board of Scientific Advisors of the National Cancer Institute, for his leadership of the authoring committee. The resulting document, entitled, "Drug Safety & Drug Efficacy: Two Sides of the Same Coin" is a proposal for improving drug safety, ensuring new drug access, and strengthening the FDA. I would like to ask that a copy of the full report be submitted to the record as an addendum to my testimony, and I would like to briefly discuss some of the recommendations.

A Systematic Approach to Safety Surveillance

It is most important for patients that FDA continuously evaluate both safety and efficacy when determining public access to new products. At the level of medical practice, safety and efficacy are always considered together by the treating healthcare professional in the context of a patient's specific circumstances and preferences. The regulatory process should reflect this essential balance that is fundamental to all medical decision-making.

Because it is impossible to know everything about a drug at the time of approval, it is important to monitor the safety and effectiveness of drugs as they are used in the general population. To strengthen the effectiveness of the current post-market system, the agency needs to develop and implement a more systematic and automated approach to safety surveillance.

By utilizing drug safety and efficacy information from a variety of sources, such as established healthcare networks like Kaiser or UnitedHealth Group, the FDA could actively identify, evaluate and respond to signals more efficiently. New policy should shift the emphasis of drug safety away from solely risk management, and instead focus upon systematic benefit-risk assessment based on comprehensive and valid information provided by the healthcare community.

Currently, a great deal of drug safety evaluation is based upon the limited data available in the New Drug Application. A locked focus on safety at this early point in a drug's life cycle would increase the amount of pre-market data required, with the likely result of stifling or unnecessarily slowing patients' access to potentially beneficial medicine. The recent IOM report on drug safety states, "to expect that pre-market studies or FDA review of these studies can reveal all the information about the risks and benefits of new drugs that is needed to make optimal treatment decisions would occasion unreasonable delay in approval." [2]

It would be far better to utilize available data mining techniques and other potential new information sources to identify unanticipated adverse events sooner following product launch and adoption in medical practice.

New policy should focus on efficiently and accurately identifying unexpected serious adverse events in a scientifically rigorous manner. Once a serious signal has been identified, FDA should have the tools to react in a proper manner that will protect the public while ensuring responsible access for patients who may depend on a particular drug. Such an approach would benefit all stakeholders.

Enhanced Technology Infrastructure

With the proper resources to improve the technology infrastructure, FDA could routinely and systematically evaluate data from completed and ongoing clinical trials and registry studies, perform useful epidemiological studies, and characterize population subtypes and their response to treatments.

In addition, greater ability to compare and combine data across different sources would result in greater flexibility and improved efficiency and the potential to generate novel insights about vulnerable populations. This includes the ability to share information regularly with the Center for Medicare and Medicaid Services and with sister agencies within the Public Health Service, including the National Institutes of Health and the Centers for Disease Control and Prevention.

Increase Training and Personnel

Just as FDA needs enhanced infrastructure and information systems, it also needs adequate personnel training to meet emerging technology advances. Increasing the number of IT trained staff is essential for the overall advancement of the bioinformatics systems. As the agency strives to monitor and evaluate the treat-

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2 Institute of Medicine of the National Academies. "The Future of Drug Safety: Promoting and Protecting the Health of the Public" Sept. 26, 2006.

ments of the future, it is imperative that FDA have the resources to effectively manage and interpret the wealth of information currently available.

FDA needs to attract and retain a greater number of professional staff with the training required to perform accurate benefit-risk assessment, evaluate new therapies and implement scientific initiatives. As the FDA workload grows, so too must the resources to recruit and increase staff with critical competencies. Increased training of FDA personnel will also enhance agency effectiveness and standards.

FDA experts could play an integral role in the development of advanced clinical trial designs that achieve greater efficiency and permit definitive conclusions to be obtained more quickly. Such advancements to the current clinical trial system could result in improved pre-market product evaluation, smaller trial sizes, more efficient dosing determinations, and ultimately, safer products reaching patients faster.

INTEGRATING NEW SCIENCE THROUGH THE CRITICAL PATH INITIATIVE

As science progresses and new treatments emerge from laboratories and clinics around the world, FDA must be equipped to perform accurate and efficient evaluation and continue its science-based tradition. It is imperative that resources be devoted to increase the support for the Critical Path Initiative to modernize FDA.

A central goal of the Critical Path Initiative is to provide tools to identify patients who will most likely respond to particular treatments, thereby improving the risk to benefit ratio. As this is accomplished, there will be new ways to diagnose, treat, cure or prevent disease and allow life-saving therapies to reach patients faster while reducing the overall cost of healthcare in the country.

Legislation introduced by Senators Kennedy and Enzi, and recently considered by the Senate, would create the Regan—Udall Foundation for the Food and Drug Administration. This will establish a leading organization for the advancement of the Critical Path Initiative and foster the advancement of the science of drug safety through public-private partnership.

NIH initiatives and collaborative research partnerships should place high priority upon the identification and use of biomarkers to (1) determine the role of genetic polymorphisms in causing drug toxicities; (2) establish effective strategies for selecting patients for treatment with specific drugs and (3) identify early biomarkers of drug benefit. The sub-populations most susceptible to an adverse event could be identified by detecting the presence or absence of a biological indicator.

Further integrating science into the regulatory process will aid researchers who design drugs, experts who evaluate their safety and efficacy, health care providers who prescribe medicine, and most importantly patients who will benefit from continued medical discovery and more effective application of new treatments.

Conclusions

In conclusion, we remain extremely supportive of the goal to improve our drug safety system and we believe that we can best achieve this goal through a science-based approach, taking into full account the voice and perspective of patients. Scientific advancements have led to better methods of disease treatment, early detection and prevention, and such technological advancements can translate to identifying safety signals more accurately and efficiently.

Increased funding for the FDA will help the agency access and utilize these tools to assess the benefits and risks of medical therapies and, in turn, help patients make the most informed decisions about the treatment options available to them.

A wide range of treatment options should and must remain available to patients. While we, of course, want safer drugs, we caution against unintentional consequences that could remove or slow access to valuable therapies without actually improving their safety. Of even greater detriment would be discouraging the future innovation of potentially life-saving new products altogether.

We applaud the committee for holding this important hearing and we welcome further, thoughtful policy discussions toward ensuring that FDA has the resources and tools it needs to advance the science of drug safety while it continues its important work to evaluate and approve new therapies for patients in need.

We look forward to continuing to work with all of you to ensure that the lives and hopes of patients continue to improve through sound, science-based, and patient-focused FDA policy. Thank you for the opportunity to speak to you today. I look forward to answering any questions you may have.

Mr. PALLONE. Thank you. Dr. Ellenberg.

STATEMENT OF SUSAN ELLENBERG, UNIVERSITY OF PENNSYLVANIA SCHOOL OF MEDICINE, SPEAKING AT THE REQUEST FOR THE COALITION FOR A STRONGER FDA

Ms. ELLENBERG. Mr. Chairman and members of the committee, I am Susan Ellenberg, professor of biostatistics and associate dean for clinical research at the University of Pennsylvania School of Medicine.

Prior to my current appointment, I directed the biostatistics and post-market surveillance programs at the FDA's Center for Biologics Evaluation Research from 1993 to 2004. I also recently served on the Institute of Medicine committee on the assessment of the U.S. drug safety system.

During my career with the FDA, I was deeply involved in one of FDA's most important functions, monitoring the safety of medical therapies after they had been approved for marketing. As such, I want to thank the committee for inviting me here today to testify on the important issue of drug safety.

Although there are many aspects of drug safety that the committee is looking at, I am going to speak particularly from my own knowledge and experience about one aspect of FDA's drug safety program that I feel most strongly about, and that is its resource needs to carry out its congressionally-mandated responsibilities.

As you know and as others have said today, there is no such thing as a totally safe drug. All drugs pose some risk to patients. Drugs are deemed safe when it appears that their benefits outweigh their risks in a given population, safe enough.

The approval for marketing a new drug or vaccine is only the beginning of a drug's lifecycle. It is critical drugs be monitored once on the market. Drug manufacturers', physicians and the FDA continuously watch for signals that a drug poses greater risks than originally believed or it may be unsafe in certain patient populations, or require special restrictions to control hazards that would otherwise cause FDA to remove it from the market.

For some years now, FDA scientists have recognized a growing resource imbalance between the agency's pre-market drug review program and its post-marketing safety surveillance capabilities. This imbalance has resulted from enactment of Congress of the Prescription Drug User Fee Act, which has greatly enhanced and enlarged FDA's pre-market drug review program and a parallel lack of increased funding for FDA's post-market drug safety program.

The recent Institute of Medicine report, "The Future of Drug Safety: Promoting and Protecting the Public Health," which I am sure many or all of you have seen, noted this resource imbalance and concluded that our drug safety system was severely underfunded. The User Fee Act has required the drug review staff at FDA to grow steadily larger to allow much more rapid review and approval of drugs than ever before. That has been a great boon to the citizens of this country, resulting in more new drugs to prevent and treat illness. But the drug safety programs at FDA have received only very limited increases in staff and funding, and thus these programs have continually lost ground in their ability to monitor the rapidly increasing number of new drugs on the market.

Further, the volume of adverse event reports submitted to the FDA has increased steadily. As you can see on the monitor, the numbers of reports of adverse events submitted to the FDA has climbed so rapidly that they threaten the ability of drug safety staff to review and process them effectively. And we discussed this earlier, the various reasons. But in any case, the numbers have gone up quite dramatically.

One of the initiatives of which I was most proud during my tenure at FDA was a thorough reevaluation of FDA safety monitoring systems, an effort commissioned by then Commissioner Jane Henney. That assessment, which was completed in 1999, resulted in a series of recommendations for major changes in our post-marketing safety programs including, among other things, intense monitoring of newly marketed products during the initial period on the market, obtaining access to health care databases, such as those of Medicare and the VA that we have talked about today, developing a new active surveillance capacity to complement existing passive surveillance system, which also need to be improved, funding for research to improve FDA's tools for monitoring the study of medical product risks, more intense intervention such as stronger warning labels or restricted distribution of higher-risk products, and funding to conduct focus safety studies when needed.

Commissioner Henney's request for a substantial boost in FDA appropriations to fund these recommendations unfortunately were not successful. But these recommendations made by FDA staff 8 years ago are very similar to the drug safety provisions of the current Senate and House bills that are currently being considered, and are entirely consistent with the recommendations of the recent IOM report. If the necessary funding had been provided at that time, the proposed programs would be up and running today and might have permitted much more rapid identification of many, if not all, of the recent drug safety problems that we have been experiencing, meaning far fewer individuals would have been exposed to excess risk.

And so, Mr. Chairman, I urge you to set as one of your highest priorities this year provision of the necessary resources to FDA's drug safety programs. I thank you very much for inviting me to present my views.

[The prepared statement of Ms. Ellenberg follows:]

STATEMENT OF SUSAN S. ELLENBERG

Mr. Chairman and members of the committee. I am Susan S. Ellenberg. Prior to my current appointment as professor of biostatistics and associate dean for clinical research at the University of Pennsylvania, I directed the biostatistics and postmarket surveillance programs at the Food and Drug Administration's Center for Biologics Evaluation and Research from 1993 through 2004. That Center, as you may know, is charged with assuring the safety of biological drugs, blood and blood products, and vaccines, and works closely with FDA's other programs for approving and monitoring pharmaceuticals. I also served on the recent Institute of Medicine Committee on the Assessment of the U.S. Drug Safety System, and am associate editor of Clinical Trials (the official journal of the Society for Clinical Trials) and of JNCI (Journal of the National Cancer Institute).

During my career at the FDA, I was deeply involved in one of FDA's most important functions—monitoring the safety of medical therapies after they have been approved for marketing. As such, I wish to thank the Committee for inviting me here today to testify on the important issue of drug safety, an issue that the Committee will be considering this year as part of its effort to reauthorize the Prescription

Drug User Fee Act. Although there are many aspects of drug safety that the Committee is examining, I have been requested by the Coalition for a Stronger FDA to speak in particular, from my knowledge and experience, about one aspect of FDA's drug safety program—its resource needs to carry out its Congressionally-mandated responsibilities.

BACKGROUND

As you know, there is no such thing as a totally "safe" drug—all drugs pose some risk to patients. Drugs are deemed "safe" when it appears that their benefit outweighs their risks in a given population. The approval for marketing of a new drug or vaccine is only the beginning of a drug's "life cycle." It is critical that drugs be monitored once on the market—drug manufacturers, physicians and the FDA continuously watch for signals that a drug poses greater risk than originally believed, may be unsafe in certain patient populations, or requires special restrictions that must be imposed so as to control hazards that would otherwise cause FDA to remove it from the market.

A RESOURCE FOR IMBALANCE

For several years now, FDA scientists have recognized that there has been a growing resource imbalance between the agency's premarket review program for drugs and its postmarket surveillance capabilities. This imbalance has been occasioned by two developments: the enactment by Congress of the Prescription Drug User Fee Act, which has greatly enhanced and enlarged FDA's pre-market drug review program, and a parallel lack of increased funding for FDA's postmarket drug safety program.

The recent Institute of Medicine Report, The Future of Drug Safety: Promoting and Protecting the Health of the Public, of which I was a co-author, confirmed those internal FDA concerns by concluding that our drug safety system was "severely underfunded." As the IOM report noted, the user fee act has required the drug review staff at FDA to grow steadily larger, which has allowed much more rapid review and approval of new drugs than ever before. That has been a great boon to our citizens, resulting in more new therapies that can prevent or treat illness. But the drug safety programs in FDA have received only very limited increases in staff or funding, and in fact have been largely held to their pre-PDUFA levels. Thus, FDA's postmarketing safety programs have continually lost ground in their ability to monitor the rapidly increasing number of new drugs on the market. Further, the volume of adverse event reports submitted to the FDA has increased steadily. As you can see from the attached FDA graphic, the number of required reports from drug sponsors of adverse events they received from physicians has climbed so rapidly that they threaten the ability of drug safety staff to review and process those reports effectively.

RESOURCE LIMITATIONS GREATLY AFFECT FDA'S CAPACITY

One of the efforts of which I was most proud during my tenure at the Food and Drug Administration was a study commissioned by then-Commissioner Jane Henney, in which she charged senior drug, device and biologics officials with a thorough re-evaluation of FDA's safety monitoring systems. That assessment, completed in 1999, resulted in a series of recommendations for major changes in our post-market safety programs, including:

- Closer monitoring of newly marketed products, particularly those for which safety "signals" suggest greater risk
- Obtaining access to health care databases, such as those of the Medicare program and the Veterans Administration
- Development of a new active surveillance capacity, to complement the existing passive surveillance systems (which would also be improved)
- Funding for epidemiological and methodological research to improve FDA's tools for understanding medical product risks
- More intense intervention in higher risk products identified by postmarket surveillance as needing special attention, such as stronger warning labels or restricted distribution, and
- Funding to conduct focused safety studies when needed

Commissioner Henney requested a substantial boost in FDA appropriations to fund these recommendations, the implementation of which would clearly have required a substantial increase in FDA's safety surveillance staff, but these requests unfortunately did not yield any additional funding .

Ironically, those recommendations are very similar to the drug safety provisions of the current Senate and House bills that are being considered along with the Prescription Drug User Fee Act. I ask you to imagine, Mr. Chairman, the frustration of the FDA drug safety staff who were denied the capacity to make those improvements, only to see the very same concepts emerge years later in Congressional legislation. One can also imagine that we as a nation would be in a far better place if the necessary funding had been provided by Congress in those years past, as the proposed programs could be up and running today, and might well have permitted much more rapid identification of many, if not all, of the recent drug safety problems that we have experienced, meaning that far fewer individuals would have been exposed to excess risk.

In conclusion, Mr. Chairman, while there are many, many issues that the Committee must grapple with in considering drug safety legislation this year, I urge you to make resourcing the drug safety programs at FDA one of your highest priorities. The agency's scientists very much want to make the kinds of improvements you are contemplating, and will do so with intensity and enthusiasm if you provide to them the staff and resources to carry out your mandate.

Thank you for inviting me to present my views on this important matter.

Mr. PALLONE. Thank you. Dr. Loew.

STATEMENT OF CAROLINE LOEW, SENIOR VICE-PRESIDENT, SCIENTIFIC AND REGULATORY AFFAIRS OF THE PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA

Ms. LOEW. Thank you. Mr. Chairman, Ranking Member Deal, and members of the subcommittee, I want to thank you for the opportunity to testify today about the vitally important issue of maintaining the safety of Americans' medicine supply. My name is Dr. Caroline Loew, and I am the senior vice president of scientific and regulatory affairs at the Pharmaceutical Research and Manufacturers of America, or PhRMA.

PhRMA shares the view of the importance of drug safety. It is also a top priority for all our member companies. PhRMA is committed to working with the Food and Drug Administration and all other stakeholders to continually improve our drug safety system in a way that preserves innovation and patient access to medicine.

As we address this critical topic, however, it is important to remember that drug safety fundamentally involves a balance between benefit and risk. Neither can be considered in isolation. Firstly and most importantly, we support the FDA's proposal to reauthorize the Prescription Drug User Fee Act, also known as PDUFA, because it most effectively addresses the issues that are critical in improving drug safety in America today.

The PDUFA proposal will make a good system even better by addressing FDA's most pressing drug safety needs: additional resources and access to the latest scientific tools and technologies. The current drug safety is stronger but could be made even stronger by the passage of PDUFA. The agency already has robust and effective systems in place for drug approval and monitoring of medicines once they are on the market. Drug safety is an extensive ongoing process that starts long before a medicine enters the market and continues long after it has been made available. It does not begin with or end when the new medicine is approved.

Before patients can receive new medicines, they undergo rigorous safety and effectiveness testing and evaluation. It often spans 10 to 15 years. Drug safety, or more precisely the benefit/risk balance, is only determined after extensive testing in laboratories, animals,

patients, and after FDA regulators have studied tens of thousands of pages of scientific data for each drug.

In fact, fully one-half of FDA's drug review project is devoted to drug safety. Agency officials also have broad statutory authority to monitor and ensure the safety of drugs after they are approved. There are extensive adverse event reporting requirements, annual reports filed by companies, and for the vast majority of approvals, post marketing studies are conducted.

The impact of this systems is undeniable. Over the last two decades, only about 3 percent of the medicines approved for the American market have been withdrawn for safety reasons. That is an enviable record by any estimation. It is also important to note that drug safety assessments today are more effective than ever before, thanks to new scientific tools and technologies.

What we need to do now to improve drug safety is to continue developing and better utilizing these new modern techniques, and we need more resources devoted to drug safety. The PDUFA proposal that FDA has put forward would help advance these crucial goals. It would provide about $150 million over 5 years to hire 82 additional staffers for post-market drug safety activities, and it would increase the use of large medical databases, which contain a wealth of drug safety information.

The proposal put forward by the FDA also addresses all of the Institute of Medicine's most important recommendations for more agency resources and improvements in the science of drug safety. Any additional drug safety reforms considered by Congress should strengthen FDA's product oversight capabilities without harming innovation or access to medicines.

PhRMA would support very targeted legislative revisions that clarify FDA authority in the areas of clinical drug exposure, post-market studies, labeling and distribution restrictions. For their part, PhRMA and its member companies have contributed to the drug safety improvement effort in recent years by initiating a number of major programs from clinical trial disclosure to biomarket research to research studies on new drug safety tools and methodologies to training programs for better adverse event detection and reporting.

In the end, we all want the same thing: the timely delivery of safe and effective medicines to patients suffering from a wide range of medical conditions and diseases. We have a system that is accomplishing that critical goal. FDA does need more resources to increase the use of today's modern technology. And that is what the FDA's PDUFA proposal would provide, and we urge Congress to reauthorize the PDUFA proposal as quickly as possible.

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 J. 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

HEARING ON

"ASSESSING THE SAFETY OF OUR NATION'S DRUG SUPPLY"

May 9, 2007

A. Introduction

Mr. Chairman and members of the Subcommittee, thank you for the opportunity to testify today on issues surrounding the safety of the nation's drug supply. 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 drug safety to be a top priority and support a number of initiatives and recommendations for improving the Food and Drug Administration's (FDA's) postmarket surveillance system, such as increased use of large medical databases and pharmacoepidemiology studies, which I will discuss in more detail later in my testimony. 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. PhRMA appreciates the opportunity to provide our views to this Subcommittee on this critical issue.

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

1. 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.
2. 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.
3. 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.
4. 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.

B. <u>The FDA's Current Drug Safety System Is Robust and Effective</u>

From the approval process through post-market surveillance, the current system, has and continues to work well in protecting Americans from dangerous drugs. Over the last 20 years, about 97 percent of all prescription medicines approved for patient use in the U.S. have safely remained on the market, while only about three percent of medicines have been withdrawn for safety reasons.

Before a drug is ever allowed on the market, it must undergo a rigorous premarket testing and approval process that often spans between 10 to 15 years. Drug safety is studied early in the development process through a series of laboratory tests, animal tests, and then with very small numbers of volunteer patients. Only after it is clear that the safety issues can be managed will it be tested in larger numbers of individuals in carefully controlled, monitored studies known as "clinical trials." Once this extensive testing process is concluded, FDA regulators then examine tens of thousands of pages of scientific data from these trials, and carefully weigh the benefits and risks of each medicine. FDA devotes fully half of its pharmaceutical review budget to safety issues in the pre- and post-market settings. Furthermore, for every 5,000 compounds that could become drugs, only five ever make it to a Phase 3 clinical study on patients, and only one is ever approved for sale by the FDA.

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 previously 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.

Pharmaceutical companies likewise play a critical role in assessing new and emerging risks with marketed medications. They spend considerable resources and have dedicated teams of experienced physicians and scientists whose jobs are to collect and analyze safety data on a daily basis - and immediately report any potential problems to government authorities. In many cases, this pharmacovigilance work includes post-approval safety studies, registries and pharmacoepidemiologic assessments of treatment populations.

FDA has broad statutory authority to monitor and ensure the safety of drug products after approval through adverse event reporting, annual reports (including new non-clinical and clinical data), and post-marketing study requirements.[1] FDA regulations require all manufacturers of prescription drug products to submit reports to FDA of adverse events associated with the use of their products.[2] Adverse events that are "serious and unexpected" (meaning that the event is serious and is not listed on the approved drug label) must be reported to FDA within 15 days of the initial receipt of the information by the manufacturer. Moreover, the manufacturer must promptly investigate these "serious and unexpected" adverse events and submit follow-up reports within 15

[1] *See* 21 U.S.C. §§355(k), 355a, 355c, 356, 356b.
[2] *See* 21 C.F.R. §§310.305, 314.80.

days of receiving new information. All other adverse events must be reported to FDA at quarterly intervals for the first 3 years after the date of approval, and annually thereafter.

FDA regulations also require manufacturers to submit an annual report within 60 days of the anniversary date of approval of a drug.[3] The annual report must contain, among other things, a summary of "significant new information from the previous year that might affect the safety, effectiveness or labeling of the drug product.[4] The annual report must contain both published and unpublished reports of "new toxicological findings" in animal and *in vitro* studies (e.g., animal studies bearing on the cancer risk of the drug).[5] Finally, the annual report must include any new clinical studies of the approved drug product, regardless of whether the study is published or unpublished.[6]

FDA also look for information on safety in large medical databases maintained by health plans and others. Access to these databases is costly and typically is purchased by the FDA and pharmaceutical companies. While these databases contain a wealth of safety information and can be used to conduct targeted epidemiological studies of particular drug risks, FDA is limited because of cost and the fact that there are no accepted "best practices" for conducting these types of epidemiological studies.

Postmarketing studies also provide useful safety information. Before or after granting marketing approval, FDA may ask a pharmaceutical company to conduct a "Phase 4" or "postmarketing study." Indeed, FDA routinely requests sponsors to conduct postmarketing studies as a condition of approval. A request is made if FDA concludes that additional information, while not essential for approval, is important in improving

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[3] *Id.* §314.81.
[4] *Id.* §314.81(b)(2)(i).
[5] *Id.* §314.81(b)(2)(v).
[6] *Id.* §314.81(b)(2)(vi).

the prescribing and use of the product; product quality; or consistency in product manufacturing. Postmarketing studies may confirm existing data, raise or answer questions, or provide new data.[7]

In a 2004 study conducted by the Tufts Center for the Study of Drug Development, researchers found that between 1998 and 2003, FDA requested postmarketing studies in the vast majority of new drug approvals – 73%. Moreover, these requests for postmarketing studies are stringent, averaging 4.4 studies and 920 patients per new drug.

A recent FDA report on the performance of pharmaceutical and biologic firms in conducting post-marketing studies shows pharmaceutical companies are meeting their postmarketing study commitments. The report indicates that, of the studies concluded between October 1, 2005 and September 30, 2006, sponsors failed to meet study commitments only 5% of the time.[8] Likewise, the report indicates that only 3% of open studies for NDAs and ANDAs were delayed, meaning that the great majority of such studies – 97% -- had been submitted to FDA, were no longer needed or feasible, or were proceeding according to the schedule agreed to between the sponsor and FDA. These results demonstrate a commitment to postmarketing safety.[9]

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[7] FDA can require sponsors to conduct postmarketing studies for accelerated approval products or for other products to assess use in pediatric populations. 21 U.S.C. §§355c, 356.

[8] 72 Fed. Reg. 5069 (Feb. 2, 2007).

[9] Critics often contend that sponsors fail to even initiate studies in the vast majority of cases. These criticisms are based on a misunderstanding of FDA's statistics. While it is true that 71% of open commitments are considered "pending," these "pending" studies are in the preparatory phase of clinical trial development during which the protocol is drafted and submitted to FDA, IRB approval is obtained and the sponsor begins recruiting clinical investigators. *See, e.g.,* FDA Response to Congressman Markey at 5 (March 30, 2005) (clarifying that typically when a study is "pending" FDA and the applicant "are working together to design a study that will adequately address the objective of the commitment"). If sponsors simply failed to initiate such studies, the studies would be coded as "delayed" rather than "pending." However, only 3% of open studies are considered to be "delayed."

C. PhRMA Supports Efforts to Improve FDA's Drug Safety System

PhRMA believes that FDA's most urgent need is not for additional authority; rather, FDA's drug safety system could be improved with additional resources devoted to postmarket surveillance activities and a more modernized approach that takes full advantage of the latest scientific tools and resources, such as large medical databases and epidemiological expertise. PhRMA believes that the PDUFA-IV proposal addresses the FDA's most pressing drug safety needs.

PhRMA supports the FDA's proposal to reauthorize the Prescription Drug User Fee Act (PDUFA-IV) because it includes important new provisions and resources to enhance and modernize the drug safety system; increase FDA's oversight of direct-to-consumer (DTC) advertising; and facilitate the timely review of innovative medications. The PDUFA-IV proposal provides approximately $150 million of new money over five years to allow FDA to (1) hire 82 additional staff for postmarket 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. This modernized approach should allow FDA to identify and assess safety risks more quickly and accurately.[10]

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[10] While PhRMA and its member companies would prefer to see FDA's review and postmarket safety functions funded primarily through general appropriations rather than user fees, PhRMA recognizes that this may not be feasible given current federal budget constraints. In order to ensure that the FDA is adequately funded to perform its critical functions of expediting the development of life-saving medications while protecting the public health, PhRMA supports the FDA's current proposal even though it includes substantial increases in user fees. PhRMA would encourage Congress to explore options for reducing or

1. The PDUFA-IV Proposal Addresses All Relevant Recommendations of the Institute of Medicine (IOM)

While the PDUFA-IV proposal does not (and should not) address FDA's internal culture or possible new authorities, it does address the IOM's most important recommendations: the need for additional resources and improvements in the science of drug safety (see Exhibit A). Under PDUFA-IV, FDA will get more funding for drug safety activities and will markedly increase its scientific expertise and resources devoted to drug safety. This, in turn, will create a better, more responsive surveillance system.

Under the PDUFA-IV agreement, FDA will get an additional $150 million over five years for postmarket safety activities. With these additional funds, FDA will have the necessary resources to:

- Reduce the agency's reliance on the spontaneous reporting of adverse events and to conduct outside research to maximize the public health benefit associated with collecting and reporting adverse event information throughout a product's lifecycle (IOM Recommendation 4.1);
- Gain wider access to large healthcare databases for epidemiological studies (IOM Recommendation 4.2);
- Conduct assessments of the effectiveness of RiskMAPs, with input from industry, academia and others, to identify risk management and communication tools that are effective (IOM Recommendation 4.4);

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eliminating the Agency's reliance on industry user fees by the time the PDUFA program is scheduled for reauthorization in 2012.

- Hire 82 new employees, including experts in epidemiology (IOM Recommendation 4.6); and
- Develop a guidance document on epidemiological study best practices that will serve as a base for agency, academia and industry use (IOM Recommendation 4.6).

In addition, and as recommended by the IOM Report (IOM Recommendation 3.5), the PDUFA-IV proposal includes numerous safety-related performance goals. These include:

- Developing a 5-year plan describing agency activities that will lead to enhancing and modernizing FDA's drug safety system;
- Conducting a study on the value of adverse event reporting;
- Developing best practices for epidemiology studies;
- Developing and validating risk management and communication tools;
- Enhancing and improving coordination between the review divisions and the Office of Surveillance and Epidemiology;
- Developing guidance for industry on choosing proprietary names that do not pose a risk of confusion with existing drug names;
- Reviewing proprietary names within specified timelines to avoid confusion and potential medication errors;
- Reviewing DTC television advertisements within specified timelines to ensure compliance with regulatory requirements.

2. PhRMA Supports FDA's PDUFA-IV Proposal Because It Will Significantly Enhance FDA's Ability to Monitor Postmarket Drug Safety

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. Prior to passage of PDUFA-I in 1992, the average review time for a new drug application ("NDA") had increased to over 30 months, and there was a significant backlog of pending NDAs at the Agency. As a result, life-saving medications routinely were available to patients in Europe well before they were available to patients in the United States. With the increased funding provided under the PDUFA program, FDA was able to hire additional staff and quickly eliminated the backlog of pending NDAs. In addition, FDA made great strides to complete its reviews of new NDAs in a more timely manner, which not only added predictability to the drug review process but more importantly benefited patients by providing quicker and more widespread access to life-saving medications, such as treatments for HIV infection. The PDUFA program was reauthorized in 1997 and 2002.

Since PDUFA was originally enacted in 1992, FDA has approved more than 1,000 new drugs and roughly 100 new biologics, including new medicines for cancer (62), metabolic and endocrine diseases (109), anti-infective drugs (96), neurological and psychiatric disorders (103), and cardiovascular and renal disease (73).

It is important to stress that throughout the PDUFA programs of the past 15 years, the exacting standards by which FDA evaluates NDAs and BLAs have been maintained and, as a result of increased funding for drug safety, even strengthened. With more

resources provided by PDUFA, FDA has been able to complete its rigorous reviews more quickly and efficiently while maintaining its high standards for safety.

That tradition continues with the latest FDA proposal for the reauthorization of the PDUFA program. The Agency's PDUFA-IV proposal contains important new provisions and resources to (1) enhance and modernize the FDA drug safety program; and (2) add a new user fee program to give FDA additional resources to review and provide advisory opinions on direct to consumer television advertisements. PhRMA believes that 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 gold standard.

A key patient safety initiative is the allocation of a portion of this funding to improving the trade name review process. Trade names are reviewed within FDA's drug safety office to help ensure that new trade names cannot be confused with existing trade names in an effort to reduce possible medication errors. FDA will now have additional resources to review trade names during drug development and provide industry with guidance on "good naming practices." This will improve the predictability of the trade name review process.

The FDA's PDUFA proposal also includes a new user fee for DTC television advertisements. In 2005, PhRMA issued a set of voluntary guiding principles regarding DTC advertising. In those guiding principles, PhRMA member companies committed to submit all new DTC television advertisements to FDA prior to public dissemination to ensure that FDA's suggestions could be addressed before the advertisement was seen

widely by the public. The proposed new user fee would ensure that FDA has the necessary resources to review pre-submitted DTC television advertisements in a timely and predictable manner prior to public dissemination. This, in turn, will create incentives for companies to voluntarily submit advertisements prior to public dissemination, consistent with PhRMA's Guiding Principles.

The PDUFA program is vital to ensuring that FDA has the necessary resources to perform its critical functions of fostering drug development and innovation and protecting the public health. The PDUFA-IV proposal in particular will provide FDA with substantial new funding to enhance its oversight over drug safety and DTC advertising while ensuring that the drug review program is as robust and efficient as possible so that patients are not left waiting for needed cures.

3. PhRMA Supports Additional Activities to Improve Drug Safety

Over the past several years, PhRMA and its member companies have demonstrated a commitment to improving drug safety and transparency both before and after approval. For example, PhRMA has established a publicly available database of clinical study results; launched a Biomarkers Consortium in partnership with the FDA and the National Institutes of Health (NIH); is working to establish accredited training programs for physicians and other healthcare providers to better detect and report adverse drug events; is undertaking an extensive methodological study to develop a structured, transparent, semi-quantitative framework for the benefit-risk assessment of drugs over the full product lifecycle and has sponsored two academic studies to validate methodologies for datamining of large databases. These activities are described briefly below.

Clinical Study Results Database. PhRMA and its members support increased transparency of clinical trial information. In 2002, PhRMA issued its *Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results* (Clinical Trial Principles). Among other things, the Clinical Trial Principles announced the pharmaceutical industry's strong commitment to the "timely communication of meaningful results of controlled clinical trials of marketed products or investigational products that are approved for marketing, regardless of outcome." In other words, industry committed to communicate results regardless of whether they were positive, negative or inconclusive.

In 2005, PhRMA established a free, publicly available internet database to allow widespread access to company clinical trial results as described by our Principles, including unpublished results. The website can be accessed at www.clinicalstudyresults.org. As of late April 2007, the PhRMA website contained thousands of individual study results for approximately 331 different prescription drug products from 50 companies. More studies and drugs are added every week. The PhRMA website thus has been extremely successful in increasing the transparency of clinical trial results.

The pharmaceutical industry also supports expanding existing clinical trial registries to facilitate patient access to ongoing clinical trials. The primary purpose of a clinical trial registry is to inform patients who may have exhausted all other treatment options about ongoing clinical trials that they can participate in. The existing government database is limited to drugs intended to treat serious or life-threatening diseases or

conditions. In 2005, PhRMA adopted a position that companies should register all non-exploratory trials regardless of the condition or disease studied.

The Biomarker Consortium: This Consortium is an innovative, unique public-private biomedical research partnership between the NIH, FDA, PhRMA and the Foundation for the NIH, created to search for and to validate new biological markers, or biomarkers.

Biomarkers are important tools that are desperately needed to improve the flow of new healthcare technologies, medicines and diagnostics. Biomarkers can be predictors of a clinical outcome, be it the effectiveness of a drug, or a safety-related outcome (e.g. a certain type of side effect), and as such their use increases the timeliness, quality and accuracy of information collected during drug development. In just one example of their use, certain biomarkers can be used to indicate whether a patient will or will not respond to a treatment. This type of personalization ensures that only patients who are likely to experience a favorable outcome from a treatment will be exposed to it, demonstrating how biomarkers can be used to meaningfully improve drug safety. As such, these tools are critical to improving the process of discovering and developing the right medicine for the right patient, delivered at the right time, and the pharmaceutical industry is committing significant resources to their development.

The Biomarker Consortium was formed to help align all the stakeholders in the biomedical research enterprise so that they can work together, collaboratively, or pro-competitively on their highest priority and shared interest, to improve human health. The biopharmaceutical industry is committed to this effort. To date, thirteen major biopharmaceutical companies are participating in this effort with thirteen other patient

organizations, disease associations, and scientific societies to advance biomarker science critical to the future of human healthcare.

Reporting Adverse Events. Spontaneous reporting of adverse drug reactions ADRs) is useful in identifying those ADRs that occur rarely. Incorporation of these reports into company or regulatory agency databases serves as a starting point for signal identification, which then must be followed by extensive analysis and validation. One of the shortcomings of this system is the variable nature of reporting and the quality of reports. Ultimately, any database is only as good as the underlying data, and one of the chief difficulties with adverse event report databases is quality. Precious resources are often expended in contacting health care professionals regarding aspects of a report they have filed. In many instances, the reporter is unable or unwilling to provide sufficient detail for analysis. Privacy laws in some countries significantly impact the ability to get detailed information in reports that occur outside the United States. In addition, simply increasing the number of spontaneous reports is also not regarded as particularly useful. Increased reports may obscure potentially important safety signals by adding "noise" to the system.

PhRMA has been working to establish an accredited training program for physicians, medical students and healthcare providers on targeted issues designed to improve the detection of adverse events and the quality of adverse event reporting. One specific goal is training modules oriented towards both medical school students and continuing medical education (CME) programs focusing on practicing physicians and other healthcare providers. These training modules would explain the role and

responsibilities of healthcare professionals in reporting ADRs, how to identify and evaluate an ADR, and how to prepare and submit reports of high quality.

Pharmacovigilance Activities. In addition, PhRMA has worked collaboratively with the FDA and the Centers for Education and Research on Therapeutics (CERTs) in the areas of risk assessment and evaluation, benefit assessment, risk communication and drug safety. Another workshop in an ongoing series will be held later this month to explore opportunities related to proactive surveillance and other new pharmacovigilance methods. The topics at this workshop will include: use of datamining of large adverse event databases, use of active surveillance in community and managed care settings, and statistical approaches to signal identification and validation. This will make a significant contribution to the efforts of FDA, academia and industry.

Benefit-Risk: Assessing the benefit-risk profile is the central element in the evaluation of drugs at any stage of their lifecycle. Understanding and trading off benefits and risks is central to pharmaceutical research, drug development, drug review and approval, prescribing, patient compliance and measuring and validating patient-centric outcomes.

However the issue of benefit-risk assessment of pharmaceuticals is one of the most prominent challenges facing all sectors of the healthcare continuum, from those involved in developing and approving new drugs, to physicians prescribing them, to patients trying to make informed treatment decisions. Approaches to the assessment of benefit and risk, and specifically balancing the two, have evolved over time, but today remain *ad hoc* at best, and as such could benefit significantly from the development of a more structured, transparent process and methodology for this assessment. Based on this

need PhRMA, in consultation with key stakeholders (including patients, physicians, the medical research community, regulators and industry), has an initiative underway to consider how to achieve more patient-focused, innovative, benefit-risk decision making.

Validation of Data mining Tools: In drug safety, data mining could potentially alert pharmacovigilance personnel of a safety signal before it would be detected using traditional methods, particularly in the case of unusual drug-event and drug-drug-event combinations. However, there is today much confusion and uncertainty regarding the potential value of using data mining methods in drug safety. Some of this arises because in fields such as finance and industry, data mining algorithms are used to make definitive decisions about processes and actions. In drug safety, data mining methodology cannot be the final "arbiter" of drug safety, but is rather only one component of a system that relies on the human judgment of astute clinicians. Another cause of confusion is that complexity has been built into drug safety data mining algorithms in an attempt to deal with the well-recognized data quality issues of safety databases. The danger here is the temptation to assume that with greater analytical complexity and sophistication also come greater precision and accuracy. A downside to data mining, especially when applied without context, is the wasted effort, which could be substantial, spent investigating "false positive signals." In addition, there is the potential negative impact of "false alarms" on public health which could arise from the disclosure of incomplete or inappropriate analysis. As such, before data mining can be used to its fullest potential in pharmacovigilance there is a real need to critically evaluate the data mining technology within this context.

To clarify the role of data mining, PhRMA on behalf of it members has engaged two independent contractors, the University of Maryland and Prosanos Corporation, to conduct research into aspects of data mining algorithms and the safety databases to which they are applied. The goal of the research is to reduce the current confusion in the field and to provide information regarding the appropriate application of data mining methods. In the studies, which are ongoing, various data mining algorithms are being compared and contrasted and the effects that reporting sources and other secondary factors and practices may have on data mining analysis will be tested. This effort was initiated in 2006 and will be producing its first results in the middle of this year, with full results in 2008, all of which will be published in peer-review scientific journals, presented at seminars, and made publicly available to regulators and pharmacovigilance scientists.

4. New Regulatory Authorities

The IOM Report recommends granting FDA broad new powers to, among other things, mandate labeling changes, order postmarketing studies, restrict distribution and use of drug products, and prohibit advertising. PhRMA believes that FDA's existing authorities are sufficient to ensure compliance with all applicable regulatory requirements, and that FDA's greatest need in the drug safety area is not new authority but rather additional resources and a more modernized approach to postmarket surveillance, both of which are provided by the PDUFA-IV proposal. Nevertheless, PhRMA would support targeted revisions to the Federal Food, Drug and Cosmetic Act (FFDCA) to clarify FDA's authority provided such revisions do not impede innovation or interfere with patient access to needed medications.

Clinical Trial Registries and Databases. PhRMA and its member companies are committed to the transparency of clinical trial information and 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.

Clinical trial registries and results databases should balance the need for transparency with the need to protect confidential commercial information. Protections for trade secrets and confidential commercial information are vital for any innovative and highly competitive industry. When government policies weaken these important protections, they also weaken the incentives for companies to continue to innovate. In the pharmaceutical industry, such policies can have significant negative impacts on the public health. It is thus essential for policymakers to carefully balance the need for greater transparency against the need to protect confidential commercial information.

Finally, any federal requirement for a registry or database should preempt inconsistent state laws in order to foster uniformity and avoid confusion among patients

and their healthcare providers about where to find complete and relevant clinical trial information.

Postmarket Study Authority. PhRMA supports granting FDA explicit statutory authority to require a postmarketing 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 postmarketing study is necessary to assess the significant new risk; and (c) the information expected to be obtained from the postmarketing 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, postmarketing 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 before being ordered to conduct a postmarketing study (e.g., label change).

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 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 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 would not only interfere with the legitimate practice of medicine but 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.

D. Conclusion

The evaluation of drug safety is an iterative process that continues throughout the lifecycle of a drug product, from earliest development, through clinical testing and approval, and continuing after approval during use by a diverse population. New information about the risks of a drug is constantly emerging and must be balanced against the known benefits of the drug. It is important to remember that drug safety cannot be

viewed merely in terms of a drug's risks; rather, it must be seen as a balance between a drug's risks and its benefits.

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 Risk Evaluation and Mitigation Strategy (REMS) proposed in some bills, 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.

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 in a relatively straightforward manner 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.

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. We believe that significant strides already have been made with the PDUFA-IV proposal, and we ask you to reauthorize PDUFA-IV as quickly as possible.

Exhibit A
Side-by-Side:
IOM Report and PDUFA Agreement -
Science of Safety and Funding Recommendations

ISSUE	IOM REPORT	PDUFA	Done
Safety-related Performance Goals in PDUFA	Recommends that PDUFA contain specific safety-related performance goals in 2007, such as: (1) target participation rates of OSE staff in NDA review teams, (2) prepare summary analysis of AE reports for new drugs within 18 months of launch, (3) review backlog of postmarketing commitments (4) review and act on drug advertisements and promotional material within specified timeframes (Rec. 3.5)	Contains many safety-related performance goals, including: (1) Developing a 5-year plan describing agency activities that will lead to enhancing and modernizing FDA's drug safety system; (2) Conducting a study on the value of adverse event reporting; (3) Developing best practices for epidemiology studies; (4) Developing and validating risk management and communication tools annually; (5) Enhancing and improving coordination between the review divisions and the Office of Surveillance and Epidemiology; (6) Developing guidance for industry on choosing proprietary names that do not pose a risk of confusion with other names; (7) timeline for reviewing promotional material, (8) timeline for reviewing tradenames	√

ISSUE	IOM REPORT	PDUFA	Done
Adverse Event Reporting System (AERS)	Recommends improving the generation of new safety signals by having CDER (a) conduct a systematic, scientific review of the AERS system; (b) identify and implement changes in key factors that could lead to a more efficient system; and (c) systematically implement statistical-surveillance methodologies on a regular basis for the automated generation of new safety signals (Rec. 4.1)	Provides funding for FDA to conduct outside research to maximize the public health benefit associated with collecting and reporting adverse event information throughout a product's lifecycle. Completion of studies is targeted at FY 11.	√
Use of Large Healthcare Databases	Recommends that CDER improve its formulation and testing of drug safety hypotheses by (a) increasing their intramural and extramural programs that access and study data from large automated healthcare databases; (b) include in these programs studies on drug utilization patterns and background incidence rates for adverse events; and (c) develop and implement active surveillance of specific drugs and diseases (Rec. 4.2)	Provides funding for FDA to obtain wider access to large healthcare databases for epidemiological studies.	√
Public-Private Partnerships to Fund Confirmatory Drug Safety and Efficacy Studies	Recommends that HHS, working with VA and DOD, develop a public-private partnership with drug sponsors, public and private insurers, health care provider organizations, consumer groups, and large pharmaceutical companies to prioritize plan and organize funding for confirmatory drug safety and efficacy studies of public health importance (Rec. 4.3).	No provision	

ISSUE	IOM REPORT	PDUFA	Done
Evaluation of Risk Minimization Action Plans (RiskMAPs)	Recommends that CDER assure the performance of timely and scientifically valid evaluations of RiskMAPs. This should include determining whether individual RiskMAPs are effective and an overall evaluation of the strategies used and processes of CDER staff and industry sponsors for planning and implementing RiskMAPs (Rec. 4.4).	Provides funding for FDA to conduct assessments of the effectiveness of RiskMAPs with input from industry, academia, and others. A public meeting will be held in FY 08, and FDA will conduct assessments on 1-2 RiskMAPs per year.	√
Development of Risk-Benefit Analysis Methods	Recommends that CDER develop and continually improve a systematic approach to risk-benefit analysis for use throughout the FDA in the pre-approval and post-approval settings (Rec. 4.5).	No provision	
Epidemiological Expertise	Recommends that CDER build internal epidemiologic and informatics capacity in order to improve the postmarket assessment of drugs (Rec. 4.6).	Provides funding for FDA to develop increased expertise in epidemiology, including developing a guidance document on epidemiology best practices and hiring more experts in epidemiology.	√

ISSUE	IOM REPORT	PDUFA	Done
FDA's Scientific Research Capacity	Recommends that FDA demonstrate commitment to building scientific research capacity by (a) appointing a Chief Scientist; (b) designating FDA's Science Board as the extramural advisory committee to the Chief Scientist; (c) including research capacity in the Agency's mission statement; (d) applying resources to support intramural research; and (e) ensuring that adequate funding for research is requested in the annual budget (Rec. 4.7).	Provides funding for FDA's Critical Path Initiative.	√
Advisory Committees – Review All NMEs	Recommends that FDA have its advisory committees review all new molecular entities (NMEs) either prior to approval or soon thereafter to advise on drug safety/efficacy and managing risks (Rec. 4.8).	No provision	
Advisory Committees – Pharmaco-Epidemiologists	Recommends that all FDA drug product advisory committees include a pharmacoepidemiologist or other individual with comparable public health expertise in studying the safety of medical products (Rec. 4.9).	Provides funding for FDA to increase its epidemiological expertise.	√

ISSUE	IOM REPORT	PDUFA	Done
Advisory Committees - Conflicts of Interest	Recommends that FDA establish a requirement that a substantial majority (60%) of the members of each advisory committee be free of significant financial involvement with companies whose interests may be affected by the committee's deliberations (defined as involvements that currently require only disclosure, not waiver (Rec. 4.10).	No provision	
Clinical Trial Registration	Recommends that Congress require industry sponsors to register all Phase 2 through 4 trials on clinicaltrials.gov if the data from the trials are intended to be submitted as part of an NDA, sNDA or to fulfill a postmarket commitment. In addition, sponsors should be required to post a summary of the results of such trials, including (a) primary hypothesis, (b) experimental design, (c) primary pre-defined outcome measure, (d) planned and actual sample size per treatment arm, (e) number and type of serious AEs, (f) overview of results, and (g) risk-benefit summary. Recommends harmonizing registration requirements with emerging international standards, such as WHO (Rec. 4.11).	No provision.	

ISSUE	IOM REPORT	PDUFA	Done
Disclosure of Review Packages	Recommends that FDA post all NDA review packages on the agency's web site (Rec. 4.12).	No provision	
CDER Review Teams	Recommends that CDER review teams regularly and systematically analyze all postmarket study results and make public their assessment (Rec. 4.13).	No provision	
Increased Funding	Recommends that the Administration request and Congress approve substantially increased resources in both funds and personnel for FDA (Rec. 7.1). The IOM favors appropriations from general revenues rather than user fees to support new drug safety responsibilities.	Includes several million dollars per year in increased user fees for drug safety activities.	√
Independent Drug Safety Center	Strong recommendation ***not*** to create a separate drug safety center. Believes that safety and effectiveness should not be separated.	Provides increased funding for drug safety activities, which will increase staffing for the Office of Surveillance and Epidemiology (formerly Office of Drug Safety).	√

Mr. PALLONE. Thank you. Ms. Thompson.

STATEMENT OF DIANE THOMPSON, VICE-PRESIDENT, PUBLIC POLICY AND COMMUNICATIONS, ELIZABETH GLASER PEDIATRIC AIDS FOUNDATION, SPEAKING ON BEHALF OF THE ALLIANCE FOR DRUG SAFETY AND ACCESS

Ms. THOMPSON. Good afternoon, Mr. Chairman, Ranking Member Deal, and members of the committee. Thank you for the opportunity to participate in today's hearing. I am Diane Thompson, vice president for public policy and communications at the Elizabeth Glaser Pediatric AIDS Foundation. Today I am testifying on behalf of the Alliance for Drug Safety and Access, a coalition of 11 patient and provider organizations, whose members advocate on behalf of over 30 million patients, suffering from hundreds of serious and life-threatening and rare diseases. Alliance members also represent over 100,000 providers of care to children and individuals with mental illnesses.

The Elizabeth Glaser Pediatric AIDS Foundation has been focused on speeding patient access to safe medicine since its inception in 1988. The foundation's creation was sparked by Elizabeth Glaser's outrage over the lack of safe and effective options for treating her two HIV-infected children. We know this committee shares our goals of ensuring that patients continue to have timely access to new therapies while strengthening and improving the drug safety system. Simply put, we do not accept that patients should have to choose between safety and speedy access to new medications. The history of our foundation, of the HIV/AIDS community and that of many in our coalition is the story of the power of patients' contributions to regulatory and scientific decision-making.

One mom's determination to fight for her child's survival helped transform drug development for children. No one stands to benefit or lose more than patients in drug safety decisions, and patients must have a strong voice in decisions about safety and risk management.

In its September 2006 report on drug safety, the Institute of Medicine proposed a fundamental paradigm shift in this country's approach to drug safety. We agree. Attention to safety must be integrated throughout the life cycle of every drug, and it must be recognized that continuous assessment of benefit and risk is every bit as important once a product is on the market and in the hands of patients as it is during the drug review phase.

FDA must be given the authority to require drug manufacturers to continue to study the safety of products after approval, to force changes to drug labels when safety issues are uncovered, and to require that the results of clinical trials be shared with patients who, after all, are the people who make the clinical trials possible.

Giving the FDA adequate authorities and flexible tools to enforce them, including civil money penalties, will benefit both patients and the industry. By providing FDA the flexibility to impose fines for noncompliance, we can avoid the worst possible outcome for everyone: having to pull a drug from the market that still holds some benefit for some group of patients.

We also agree with the IOM's recommendation that FDA safety staff must have a greater formal role in drug review and in risk

management decisions. Finally, safety-related performance goals must be added to PDUFA. The IOM report notes that a recent study found that 21 percent of prescriptions are written for off-label uses. Any effort to reform the drug safety system that fails to address one-fifth of the use of drugs in real world settings would leave a significant safety gap, a safety gap that would particularly affect children since still far too few drugs are ever tested in children before they are allowed on the market.

The FDA's authority to require post-market safety studies must clearly and unequivocally extend to both on-label and off-label uses. We ask that the subcommittee make the public dissemination of trial results a cornerstone of its drug safety efforts by establishing a clinical trials results database. By linking the registration of new trials with final outcomes, the database would provide patients and providers with additional information with which to assess benefits and risks and could help prevent selective reporting of positive results and the problems that have resulted from the withholding of negative trial results. Given that clinical trials would not exist without patients' willingness to give of their time and health, such a mechanism could help restore patients' trust in the integrity of the clinical trials process.

For FDA to succeed in implementing these reforms, it is essential that new and expanded safety activities be explicitly paired with increased resources, both in user fees targeted to drug safety activities and in appropriations. The need for new authorities and for the increased funding are inextricably linked, and we strongly urge the subcommittee to consider these issues along with legislation to improve the safety and access of pediatric drugs and devices as a part of a single package.

Mr. Chairman, members of the committee, the committee has before it an historic opportunity to finally match our Nation's success in speeding new therapies to patients with a system that can better ensure the safety of those products once they are on the market. We appreciate your interest in the patients' perspectives on these critical issues and look forward to working with you to accomplish these goals. Thank you again for the opportunity to share our views.

[The prepared statement of Ms. Thompson follows:]

STATEMENT OF DIANE E. THOMPSON

Mr. Chairman, Mr. Deal, and members of the subcommittee, thank you for the opportunity to participate in today's hearing. I am Diane Thompson, vice president for public policy and communications at the Elizabeth Glaser Pediatric AIDS Foundation. Today, I will be testifying on behalf of the Alliance for Drug Safety and Access (ADSA), a coalition of 11 patient and provider organizations. Collectively, members of ADSA advocate on behalf of over 30 million patients, including those suffering from HIV/AIDS, Parkinson's disease, spinal cord injuries, paralysis, multiple sclerosis, leukodystrophies, Tourette Syndrome, and over 6,000 known rare diseases. In addition, our members represent over 100,000 providers of care to children and individuals with mental illnesses.

As a representative of the Elizabeth Glaser Pediatric AIDS Foundation, I am also proud to offer the perspective of an organization that has been focused on speeding patient access to safe medicines since its inception in 1988. This issue is at the heart of our mission—the Foundation's creation was sparked by Elizabeth Glaser's outrage over the lack of safe and effective options for treating her two HIV-infected children. Although Elizabeth's efforts were too late to save her daughter, Ariel, who died from AIDS at the age of 7, her legacy includes her son Jake, now 22 years old,

and the thousands of HIV-infected children around the world who now have the chance to grow up healthy and even start families of their own, thanks to the search for lifesaving pediatric medicines that Elizabeth Glaser and the Foundation championed.

I would like to thank the chairman, the ranking member, Mr. Waxman, Mr. Markey, and other members of the subcommittee for your leadership on this issue, for moving beyond the headlines to examine our nation's current drug safety system and discuss meaningful solutions to ensure that the Food and Drug Administration (FDA) remains the world's gold standard for public health protection. Your task is not an easy one and we appreciate the historic nature of this undertaking.

We have the opportunity before us to both maintain timely access of patients to new therapies, while strengthening oversight of drugs already on the market. We believe that with sufficient resources both goals are achievable. Simply put, we do not accept that patients should have to choose between safety and speedy access to new medications.

Patients with serious illnesses understand that bringing drugs to market in a timely way means that not every risk can be identified in advance. What they also demand, however, is sufficient information for themselves and their providers to assess risks and benefits on an ongoing basis—which often means further testing of the drug after approval. Yet, the FDA has virtually no authority to compel drug manufacturers to continue to study the safety of products after they have been approved, force changes to drug labels if dangerous side effects are uncovered, or require that the results of clinical trials be shared with the patients who make them possible.

Giving FDA these authorities and flexible tools to enforce them, including civil money penalties, as legislation pending before the Committee would do, ultimately benefits both patients and drug manufacturers. Allowing FDA to require additional testing of drugs postmarket could actually allow the FDA to approve drugs more quickly, knowing it will have the ability to act if there are new safety concerns once the drug is in the hands of patients. Also, by giving FDA the flexibility to impose fines for non-compliance, we can avoid the worst possible outcome for everyone: pulling a drug from the market that still holds some benefit for some group of patients.

We believe that the core of any effort to improve drug access and safety must be a shift to a "life-cycle" paradigm, with an emphasis on the continuing pursuit of knowledge about a drug's risk-benefit profile and timely communication of that information to patients and providers. This approach, which is recommended by the Institute of Medicine (IOM), has been included in drug safety legislation introduced by Mr. Waxman and Mr. Markey. In our view, individualized risk evaluation and mitigation strategies, rather than a one-size-fits-all approach to patient safety, will be key to the appropriate balancing of drug risks and benefits that is so critical to patients with life-threatening illnesses.

To further improve the depth and breadth of input into drug safety decision making, we ask the Committee also to adopt the IOM's recommendation that the Office of Surveillance and Epidemiology (OSE) be given a greater role in drug review and the development of safety plans. The lack of communication and cooperation between that office and the Office of New Drugs, highlighted in both the IOM report and a March 2006 report by the Government Accountability Office, is deeply troubling. At minimum, we recommend that the Committee formally assign OSE staff a role in the review of new drugs applications and post approval regulatory actions, as the IOM recommends.

We ask the subcommittee also to ensure that any drug safety legislation includes mechanisms for greater public input and transparency. The history of our Foundation and of the broader HIV/AIDS community is the story of the power of patients' contributions to scientific decision making. Although they began as three mothers around a kitchen table with no formal training in science and medicine, Elizabeth Glaser and the other founders of the Foundation ultimately changed the accepted thinking of both the National Institutes of Health and FDA about the risks of not studying AIDS drugs in children—a success story that is repeated throughout the histories of patient organizations. Given that no one stands to benefit or lose more than patients in drug safety decisions, we ask that you consider a significant role for patients in the assessment and management of drug risks.

We also urge the committee to clarify that any new authority of FDA to require studies of post-market safety concerns is not confined to on-label uses of the drug. In our efforts to improve the drug safety system, we need to pay particular attention to not only what happens inside the FDA, but also what goes on in the real world. A recent study found that 21 percent of prescriptions written in 2001 were for off-label uses. Any effort to reform the drug safety system that fails to address one-fifth of the use of drugs in real-world settings leaves a significant safety gap.

Children would be left at particular risk by the failure to clarify this authority, since as much as three-quarters pediatric prescribing is off-label. Thanks to the efforts of many on this Subcommittee, there are mechanisms available to both encourage and require manufacturers to study their products for children. However, there are gaps in those mechanisms. The existing pediatric study requirement does not apply to off-label uses. While the existing incentives can be applied to off-label studies, they are voluntary—and we are seeing that manufacturers are increasingly opting not to conduct the studies FDA requests. Unambiguous authority to require such studies when the off-label use is significant will help ensure that children too can reap the benefits of an improved drug safety system.

In our view the subcommittee must make the public dissemination of trial results a cornerstone of its drug safety efforts. The establishment of a results database would be a significant step forward in giving patients and providers additional information with which to assess benefits and risks. By linking the registration of new trials with final outcomes, this database also could help prevent selective reporting of positive results and the problems that have resulted from the withholding of negative trial results. And, not incidentally, given that clinical trials could not exist without patients' willingness to give of their time and health, such a mechanism could help restore patients' trust in the integrity of the clinical trials process.

While we work toward providing the FDA additional authorities and enforcement tools, we must acknowledge that chronic under-funding is severely straining the ability of the Agency to perform even its current functions. Years of essentially flat funding, coupled with new challenges such as increasingly global markets, the threat of bioterrorism, and the promise of personalized medicine, have left the Agency struggling to meet its obligation to protect the public health. We—Congress, the Administration and patients—must work together to give the FDA the resources it needs to accomplish its critical mission. We suggest the combination of an increase in user fees targeted to drug safety activities and an increase in appropriations. Because we believe that the need for new authorities and for increased funding are so inextricably linked, we strongly recommend the subcommittee consider these issues, along with legislation to improve the safety and availability of pediatric drugs and devices, as part of a single legislative package.

Mr. Chairman, you have before you a historic opportunity to finally match our nation's success in speeding new therapies to patients with a system that can better ensure the safety of those products once on the market. We appreciate your interest in patients' and providers' perspectives on these critical issues and look forward to working with you to accomplish these goals.

Thank you again for the opportunity to share our views.

Mr. PALLONE. Thank you. Thanks a lot. Mr. Theriault.

STATEMENT OF JOHN THERIAULT, CHIEF SECURITY OFFICER AND VICE PRESIDENT, GLOBAL SECURITY, PFIZER

Mr. THERIAULT. Thank you, Chairman Pallone and Ranking Member Deal and members of the subcommittee. My name is John Theriault. I am the vice president of global security at Pfizer. Prior to joining Pfizer, I was a special agent with the FBI for 25 years, retiring in 1995 as a member of the Bureau's Senior Executive Service. It is a pleasure to appear before you today to talk about a critical issue: drug safety and efforts to protect the U.S. pharmaceutical supply from counterfeit medicines.

When I joined Pfizer in 1996, the company did not have an anti-counterfeiting program, frankly because there were no indications that any of our products were being counterfeited. That changed in 1998 when we launched Viagra, and I think that understanding what happened with that product at that time will help in understanding the counterfeit medicines industry that has evolved since then.

Viagra was a unique product in 1998, and it was in great demand all over the world. But because of regulatory requirements, it was not legally available in many countries. So what we saw im-

mediately was a global demand that was filled by entrepreneurs who purchased the product in a country where it was available and resold it sometimes at 10, 20 times what they had paid for it in countries where it was not available.

Very soon thereafter, we saw our first counterfeiting case. It involved a UK organized crime figure who was convicted of conspiring to import counterfeit Viagra from a legitimate Indian company. Now, over the next few years, we conducted several investigations to identify Viagra counterfeiters and distributors. But in doing so, what we discovered was that they were counterfeiting and distributing other counterfeit medicines that we were not aware of. The Viagra investigations actually opened a door for us to look into a very robust counterfeiting industry that we didn't know existed.

Since the inception of our anti-counterfeiting program, we have discovered counterfeit versions of our medicines in more than 60 countries. The medicines span a wide range of therapeutic areas, and they include Aricept, Lipitor, Norvasc, Diflucan, Ponstan, Cabaser Celebrex, Dilantin, Vibramycin and Zoloft. This is an issue that goes well beyond erectile dysfunction drugs. It is a counterfeiting issue that affects virtually every therapeutic area you can think of.

Now, it is Pfizer's goal to make sure that every patient who buys a Pfizer product receives an authentic Pfizer product, and we consider the counterfeiting problem to be so serious today that our program to investigate and deal with it has increased from one security professional in New York in 1999 to 17 security professionals based in the United States, Mexico, the United Kingdom, Germany, Turkey, mainland China, Hong Kong, India, Thailand, and Malaysia.

To give you some idea of the scope of the problem, in 2006 alone, law enforcement and customs authorities, with whom our investigators are working, conducted 238 raids, made 501 arrests, seized over 8.1 million units of counterfeit Pfizer products and enough active pharmaceutical ingredient to manufacture more than 15 million counterfeit Viagra tablets and more than 20 million counterfeit Norvasc tablets.

During those raids, counterfeit versions of other companies' medicines were discovered as well. Counterfeiting is a serious crime, and as you can see from this display, counterfeiters take great care in replicating the appearance of genuine product. The counterfeit product there is on the left. The authentic is on the right, and it is virtually impossible to differentiate those by visual inspection.

But what you can see from the next display is that the counterfeiters don't really take quite as much care in the manufacturing process. Counterfeits are inherently dangerous. They are manufactured in unknown locations using unknown ingredients. We have seen counterfeits that contain no active pharmaceutical ingredient and therefore did not deliver the therapeutic benefits for which they were prescribed. Some contain super potent amounts of active ingredient, which increase the risks of adverse events, and yet others contain toxic ingredients that are harmful in themselves.

Our experience indicates that the counterfeit medicines problem is growing, and it is being facilitated by the Internet, which pro-

vides both business-to-business distribution capabilities as well as retail opportunities, via bogus online pharmacies.

Counterfeiters are also exploiting a loose distribution channel to get their bad medicine into the hands of patients. The evidence clearly reveals that the more times medicines change hands in the distribution system, the more opportunities there are to introduce counterfeits.

Now, I said the problem is growing, and the reason for that is simple. This is a very, very high-profit, low-risk criminal enterprise, and we shouldn't lose sight of the criminal nature of this as we debate drug safety. How profitable is this for counterfeiters? That graphic shows that if you were to invest $20,000 in a kilo of cocaine—not that anybody would do that, but that is about what it costs these days. $20,000 for a kilo of cocaine would yield $60,000 in sales. Subtract the cost, and you have got a $40,000 profit. You can buy from any Indian company on the Internet the active ingredient for Viagra, $64. That would produce 14,000 50-milligram Viagra tablets at $10 apiece, $140,000 in revenue. Subtract the $64, and you have got a much greater profit margin doing counterfeit drugs. This is a crime that attracts serious criminals.

Now, the facts here are irrefutable. The importation of counterfeit, infringing, misbranded, non-approved, pharmaceutical products in the United States is increasing exponentially. Those products, by definition, pose a risk to public health and safety. The response by regulatory and law enforcement agencies to this growing crisis has to be reviewed, analyzed and modified at all levels.

To sum up quickly, instead of discussing ways to deregulate the current safety system, we think that we ought to be discussing ways in which the current system could be improved to mitigate these threats to patients. Mr. Chairman, Ranking Member, members of the committee, thank you for the opportunity to share this with you.

[The prepared statement of Mr. Theriault follows:]

STATEMENT OF JOHN THERIAULT

Chairman Pallone, Ranking Member Deal, and members of the subcommittee, my name is John Theriault. I am the chief security officer and vice president of global security at Pfizer Inc, the world's largest pharmaceutical company. It is a pleasure to appear before you today to discuss an issue of critical importance: drug safety and efforts to protect the United States pharmaceutical supply from contamination with counterfeit products.

Prior to joining Pfizer, I spent more than 25 years as a Special Agent of the Federal Bureau of Investigation. During my FBI career I had substantial experience in international law enforcement and served for a number of years as the Legal Attache in Ottawa, Canada and London, England.

Mr. Chairman, while my testimony today focuses on our experience with counterfeit Pfizer products, I wish to impress upon the subcommittee that these problems are not limited to Pfizer. They threaten the entire pharmaceutical industry and most importantly, the U.S. patients who depend upon that industry.

As the subcommittee is well aware, there is already importation of counterfeit and diverted medicines into the United States through the mail, courier services, and some unethical re-packagers and wholesalers. Millions of Americans who assume that the prescription medicines they buy online are safe and effective are at risk. Regardless of the method of obtaining drugs from Canada or other countries, there is a real potential for fraud or harm. I would emphasize that every time a medicine changes hands represents—an additional opportunity for counterfeit products to be introduced into distribution.

COUNTERFEIT PHARMACEUTICAL PRODUCTS: WHAT IS THE SCOPE OF THE PROBLEM?

The problem of counterfeit medicines, once thought to be limited to developing countries with weak regulatory systems, is now recognized as a global problem from which no country is immune. The manufacture of counterfeits is not limited to China and India. They are produced in at least twenty-four countries, including Canada, the United Kingdom, and four other members of the European Union—Belgium, the Netherlands, Poland, and Portugal.

Since 1998, when the first counterfeit Viagra tablets were discovered in the United Kingdom, Pfizer has developed a focused anti-counterfeiting program to protect the integrity of our products and supply chain. Staffing for that program has increased from one security professional based in New York, to seventeen security professionals based in the United States, Mexico, the United Kingdom, Germany, Turkey, China, Hong Kong, India, Thailand, and Malaysia. Our Product Integrity Steering Committee has set as Pfizer's goal ensuring that every patient who buys a Pfizer product receives an authentic Pfizer product.

We are waging a fierce battle against these counterfeiters. Pfizer products targeted by counterfeiters now include Aricept (Alzheimer's disease), Lipitor (cholesterol), Norvasc (hypertension), Diflucan (antifungal), Ponstan (anti-inflammatory) and Viagra (erectile dysfunction), Cabaser (Parkinson's disease), Celebrex (pain), Dilantin (epilepsy), Vibramycin (antibiotic), and Zoloft (depression).

Although it is difficult to measure the true scope of the counterfeiting problem, the number of reported seizures by law enforcement of Pfizer products serves as a useful baseline. During 2006, authorities from 36 countries reported seizing more than 8.1 million counterfeit tablets, a 20.8 percent increase over 2005. That increase was most significant in Europe, the Middle East and Africa, where seizures increased by more than 332 percent

A CASE IN POINT: DEADLY POISON MASQUERADING AS MEDICINE

Fake medicines are costing lives. In March 2007, we heard of a tragic story of a woman's death which, according to press reports, was caused by drugs she ordered online from a bogus Canadian pharmacy. Instead of treatment for her arthritis and allergies, Ms. Marcia Bergeron was slowly poisoned by products that contained dangerously high levels of strontium, uranium, and lead, heavy metals that had apparently been used as a cheap filler. Ms. Bergeron started losing her hair and had blurred vision and died a few days after Christmas in 2006.

We fear that there may be more terrible stories like this one. I'm sure you all have read the story from Sunday's New York Times about the hundreds of deaths in Panama from cough syrup from China that contained diethylene glycol.

It is virtually impossible to see differences between counterfeit and genuine medications. If you visited the manufacturing facilities, the differences would be shockingly obvious. Drug counterfeiters do not care about safety or sanitation. They only care about profits, and counterfeiting is highly lucrative. The profitability of drug counterfeiting far exceeds that of the illicit drug trade. However, there is a lower chance that these counterfeiters will get caught, and if they do, the penalties are less punitive.

RXNORTH: PROFITS BEFORE PATIENTS

Another case involves the Internet pharmacy RxNorth. A company whistleblower told a Canadian Television (CTV) news program that customers had received expired drugs, and that the expiry dates had been covered up on packages. In addition, the drugs were not Canadian. In fact, RxNorth was filling prescriptions for US citizens with counterfeit versions of Lipitor, Celebrex and other products. The CTV news program reported that many of the drugs RxNorth sold came from sources in the UK or Australia and were shipped to a dispensing facility in Freeport, the Bahamas, where Internet orders were filled and shipped to US customers.

Counterfeiters often use a convoluted shipping path to evade the authorities and trick customers. For example, on May 22, 2006, UK Customs intercepted a four-pallet shipment of pharmaceuticals, which had come to the UK from the United Arab Emirates (UAE). The shipment consisted of eight products manufactured by five major pharmaceutical companies: Pfizer, AstraZeneca, Novartis, Merck, and Proctor & Gamble. The shipper was the Oyster Corporation, of Sharjah, UAE. The intended recipient was Missouri-Bain Thomson, of the Personal Touch Pharmacy, in Freeport, the Bahamas. Investigation by the authorities determined that Personal Touch Pharmacy computers were connected to Rx North's servers. This is commonplace: according to a 2005 FDA study, fewer than two percent of the thousands of Web sites advertising cheap Canadian drugs are actually based in Canada.

Our infrared spectral analysis of the seized Lipitor tablets showed that the Lipitor was counterfeit, and contained about 82 percent–86 percent of the claimed concentration of active pharmaceutical ingredient (API). The lot number printed on the packaging of the counterfeit Lipitor' was legitimate for a product produced for the Middle East market, and the counterfeit packaging was elegant. Pfizer analysts examined the packaging and determined that the "i" in the word "atorvastatin" on the blister foil was placed differently, indicating a difference in font size; and the breakage-line between the single cavities showed that the authentic blister has a tighter punching line than the sample. The counterfeit packaging also contained a patient information leaflet, although it was smaller than a genuine leaflet, and missing a page. The fact that the counterfeiters are using legitimate lot numbers is concerning, since it demonstrates a level of sophistication in their deception that makes the counterfeits that much harder to detect.

On June 1, 2006, Pfizer investigators notified the Bahamian authorities of the facts in this case, and on June 9th the Bahamian authorities raided the Personal Touch Pharmacy in Freeport. There they seized $3.7 million worth of products, spanning numerous different brands from 13 different manufacturers. The total amount of product seized amounted to 3.025 million dosage units of products. The Bahamian investigation determined that approximately $8 million worth of business was conducted at Personal Touch Pharmacy on a yearly basis. The investigation is ongoing.

We remain concerned that there are thousands of similar situations that remain undetected, and that consumers like Ms. Bergeron will be victims to this fraud and greed. As Congress develops drug safety legislation, it is essential that you carefully consider this very dangerous situation that has yet to be adequately addressed.

The facts are irrefutable. The importation of counterfeit, infringing, misbranded, and unapproved pharmaceutical products into the United States is increasing exponentially, and those products, by definition, pose a risk to public health and safety. The response by regulatory and law enforcement agencies to this growing crisis must be reviewed, analyzed, and modified at all levels. The public health and safety depend upon the FDA's vigilance. The FDA and Customs must receive the additional resources necessary to fulfill their current mandate. Regulations currently in existence must be fully funded and fully enforced. The notion that somehow importation can be done safely by implementing so-called anti-counterfeit technology is to ignore everything we know about counterfeiting and counterfeiters. Similarly, the notion that importation on any scale will be as safe as the current system is to ignore all of the available evidence. Again, any time a medicine changes hands presents a new opportunity for the introduction of counterfeits into distribution. Instead of discussing ways to "de-regulate" the current safety system, we ought to be discussing ways in which the current system can be improved to mitigate these threats to patients.

Mr. Chairman, Ranking Member Deal, and distinguished members of the subcommittee, thank you for this opportunity to express our concerns about this critical issue. I would be happy to answer your questions.

Mr. PALLONE. Thank you. I recognize Dr. Levine.

STATEMENT OF SHARON LEVINE, M.D., ASSOCIATE EXECUTIVE DIRECTOR, PERMANENTE MEDICAL GROUP, SPEAKING ON BEHALF OF THE KAISER PERMANENTE MEDICAL CARE PROGRAM

Dr. LEVINE. Mr. Chairman, distinguished committee members, I am a physician with Kaiser Permanente in northern California, and I oversee the Permanente Medical Groups' efforts on drug use management in partnership with my Kaiser pharmacist colleagues.

Our shared goal is the delivery of high-quality, safe and effective drug therapy and pharmaceutical services to our members. In order to do this, our physicians and pharmacists need the best available information on the safety and effectiveness of the drugs we prescribe and dispense. The importance of this issue is increasing every year. New, more powerful drugs are being approved and released to the market, and prescription drug therapy is playing an ever-increasing role in therapy.

An important benefit of our efforts to fully integrate pharmacy services with health care delivery is that we are able to capture detailed and very complete information about the drugs we prescribe and dispense since almost 98 percent of prescriptions written for Kaiser members are filled in our pharmacies at our facilities, and we are able to match that information with robust clinical and demographic data that is captured in our delivery system and our health plan.

Because of our large and stable population, we have the ability to generate enormous statistical power in research studies that we do. We have begun in earnest to utilize these data to learn more about the safety and effectiveness of specific prescription drugs and to answer questions which, when applied clinical practice, will protect consumers from drugs that pose an unacceptable risk compared to the benefits the drugs provide.

We believe strongly that there is a need for an intentional, careful, and systematic data collection and review of a drug's use, which begins with its introduction into the market. This will enable faster identification of safety problems that result from the use of the drug outside the carefully controlled circumstances of phase one through three trials—ideally before rapid uptake of the drugs in the market exposes more people than necessary to unanticipated risks.

Our researchers have access to and analyze data from multiple sources; membership records, hospital discharge records, outpatient and inpatient prescription data, outpatient clinic data, and laboratory and x-ray results. My written testimony provides detailed information on these data sources and how they are used. And I want to share with you today two examples.

The Vioxx story is obviously very well known to this committee. Almost everyone has mentioned it, and it has become the poster child for the call to protect the public from unacceptable risk. A relatively limited population of Kaiser Permanente members were exposed to this drug. We had in place a Web-based tool to enable physicians to identify the small subset of patients who actually stood to benefit from the theoretical advantage that the drug provided, that of avoiding serious gastrointestinal side effects Yet millions and millions of patients in the general population received this drug. Almost 107 million prescriptions for Vioxx were filled before the drug was pulled from the market.

In collaboration with the FDA, Kaiser Permanente researchers and clinicians were able to confirm that Vioxx increased significantly the risk of coronary events, 5 years after introduction of the drug into the market and 5 years after the VIGOR trial which first raised the issue of vascular events.

Equally important, the same prescription drug and clinical data can be used to erase safety concerns that are raised by spontaneous reports of adverse events. In March 2005, the FDA issued an advisory to physicians urging caution in prescribing topical tachrolinus and pimecrolimus, two topical agents used to treat eczema and other skin conditions, because of concerns raised by animal studies and isolated case reports in a small number of patients. Matching up our pharmacy database with our cancer registry, we were able to identify those patients who had received those two drugs and

were also diagnosed with cancer. Our researchers actually found no increase in the overall cancer rates but did find an increase in cutaneous T-cell lymphoma, a skin malignancy, among the drug users.

By examining the medical records of these patients, and excluding those that the physicians suspected of having cancer prior to the drugs, our researchers were able to find no increased risk either of cancer in general or of cutaneous T-cell lymphoma.

These are just two examples of what is possible using existing data, and my written testimony contains many more examples. In systems like Kaiser Permanente and the Veterans Administration today, the rapidly approaching future of complete clinical data capture with electronic medical record systems will significantly enhance the ability of researchers to identify and quantify problems and assess associated risk, which will inform better risk/benefit analysis.

I want to thank the committee for taking these issues under consideration and for your interest in this, and I look forward to answering your questions.

[The prepared statement of Dr. Levine follows:]

KAISER PERMANENTE®

Testimony of

Sharon Levine, M.D.

Associate Executive Director

The Permanente Medical Group, Inc.

on behalf of the

Kaiser Permanente Medical Care Program

Before the

Committee on Energy and Commerce
Subcommittee on Health
U.S. House of Representatives

May 9, 2007

Chairman Pallone, Congressman Deal, and distinguished Subcommittee members, I am Dr. Sharon Levine, a pediatrician and Associate Executive Director of The Permanente Medical Group (TPMG), which together with Kaiser Foundation Health Plan and Kaiser Foundation Hospitals make up Kaiser Permanente's Northern California Region. One of my responsibilities is to oversee our Medical Group's efforts on drug use management, and to partner closely with my Health Plan pharmacist colleagues in delivering high quality, safe and effective pharmaceutical services to our members. I appreciate the opportunity to testify here today on the important subject of prescription drug safety. No issue is more important to those of us intimately involved in providing medical and pharmaceutical care to Kaiser members than the safety of the drugs we prescribe and dispense.

I am testifying today on behalf of the national Kaiser Permanente Medical Care Program. Kaiser Permanente is the nation's largest integrated health care delivery system. We provide comprehensive health care services to more than 8.7 million members in our 8 regions, located in 9 states (California, Colorado, Georgia, Hawaii, Maryland, Ohio, Oregon, Virginia and Washington) and the District of Columbia. In each Region, the nonprofit Kaiser Foundation Health Plan enters into a mutually exclusive arrangement with an independent Permanente Medical Group to provide or arrange for all medical services required by Health Plan members.

In our organization, virtually all pharmacy services are provided directly in Kaiser Permanente facilities by Health Plan employed pharmacists. This year, the more than 15,000 Permanente physicians and their practitioner colleagues will prescribe or furnish over 65 million prescriptions and Kaiser pharmacists will dispense more than $3 billion worth of prescription drugs. Our physicians and pharmacists make their best efforts to ensure that our members receive the highest quality and most cost-effective pharmaceutical care possible based on the best and most current clinical evidence. This is supported by a strong culture of cooperation and collaboration between our medical groups and our pharmacy program.

An important and very valuable benefit of fully integrating pharmacy services in our health care delivery system is that we are able to capture detailed information about the drugs we prescribe and dispense and to match that information with other clinical and demographic data in our delivery system.

I would like to spend a few minutes discussing what this means in terms of the ability to learn more about the safety and effectiveness of specific prescription drugs and to enable our researchers (and others) to help protect all Americans from drugs that pose an unacceptable risk compared to the benefits they may provide.

All drugs are potentially "dangerous" and this is an important point for consumers to understand. Today, we are focused more narrowly on the fact that some drugs may be too dangerous considering the potential benefits they provide, and that we have not done enough to determine which drugs those are before there is aggressive marketing, rapid uptake and broad exposure to the drugs. We believe that carefully and systematically

examining data on drug use early in a drug's post-approval appearance in the market, we can better and more rapidly identify safety problems--hopefully before rapid uptake of drugs in the market exposes many people to associated risks.

For much of this testimony I owe a debt of gratitude to my colleagues Dr. Joe Selby, of Kaiser Permanente's Division of Research, and Drs. Michele Spence, Rita Hui and Jim Chan of our Pharmacy Outcomes Research Group, the talented health researchers currently using our databases to confirm or disprove suspected safety problems with specific prescription drugs. We are hoping to partner with colleagues at the FDA on several projects, and continue work on other drug safety issues of interest to Kaiser Permanente researchers and clinicians.

Drug Safety and the Use of Kaiser Permanente Databases

Background

New drugs continue to appear at an ever-increasing rate and a growing proportion of children and adults take medication regularly. There is a need to strengthen several aspects of the safety monitoring and evaluation process once drugs reach the market so that adverse effects of medications can be detected and quantified as early as possible.

Evaluation of drug safety in the U.S. has relied primarily on data from pre- (Phase I-III clinical trials for both safety and efficacy) and post-marketing clinical trials and on information collected from spontaneous reporting systems.[1,2] While clinical trials will often detect common adverse events, they are unable to identify all side effects. The size of pre-marketing trials is such that adverse events as common as 1/1000 patients often go undetected before marketing.[3] Post-marketing trials are not routinely performed and, though larger, are still insensitive to less frequent but potentially severe adverse effects. Moreover, the selection of patients for both pre- and post-marketing trials usually eliminates individuals with coexisting diseases as well as the very old and very young. These groups may be most at risk for adverse effects. Thus, results may be poorly applicable to the full population that will eventually be exposed to the drug. Another important limitation of pre-marketing trials is that they are usually of short duration (i.e., months) and therefore likely to miss adverse effects that emerge only after prolonged exposure.

The current U.S. system for post-marketing monitoring of drug safety depends extensively on the voluntary reporting of adverse events by providers, consumers, and pharmaceutical companies. This system has several limitations. It is estimated that at most only 10% of adverse events are reported to the FDA.[4] In addition, the FDA cannot estimate the risk of these events as it does not also have information on the number of individuals receiving the drug (denominators). A particular weakness of spontaneous reporting systems is the inability to identify adverse effects that are common, but are modestly increased by use of the drug (e.g., a 2-fold increase in risk). Modest increases in common events have a much greater public health impact than very rare adverse events.[5]

Deficiencies in the current approach to monitoring drug safety in the U.S. have been highlighted in recent years by reports from both clinical trials and observational studies showing an increase in risk of coronary artery disease associated with the widely used Cox-2 inhibitors.[6-12] Although myocardial infarction is a relatively common event among adults in the U.S., the association with certain of the Cox-2 inhibitors was not firmly established until the drugs had been in widespread use for more than 5 years.

Large observational, epidemiologic studies of outcomes related to use of marketed drugs are often the best means of relatively quickly evaluating risk signals detected either in smaller clinical trials or by spontaneous reports, particularly when existing clinical databases can be used to conduct appropriate studies.

Essential ingredients for efficient and valid observational studies of drug safety include a very large population that is stable, in terms of remaining under observation; that is diverse, in terms of both socio-demographic characteristics and health status; and for which accurate, automated records are available for measuring drug exposure over time, for completely capturing the occurrence of endpoints (adverse events), and for measuring clinical characteristics that may confound observational comparisons. In such a setting, many appropriate studies can be completed as longitudinal or cohort analyses. In some instances, more primary data collection will be required to measure additional predictors that could differ between persons exposed to the drug of interest and those unexposed. Ready access is needed to all relevant medical records, and occasionally to the patient population (via interviews or surveys) or to prescribing physicians, in order to measure important covariates such as indications for the medication.

Kaiser Permanente Clinical Databases

Kaiser Permanente (KP) is an integrated, prepaid, group model health care delivery system that currently has nearly 6.4 million enrolled members in California. This membership is significantly more stable than that of most other large health plans or systems, with average member tenure of more than twelve years. KP's automated administrative and clinical databases are unparalleled in their detail and completeness and therefore offer important advantages--in addition to population size--for evaluating possible adverse effects of pharmaceuticals. Chief among these advantages are the availability of nearly complete laboratory test results, both inpatient and outpatient; detailed coded data on all outpatient diagnoses and procedures (as well as complete inpatient data); rapid access to paper medical records for past and present members; a uniform electronic medical record that is currently being implemented; extensive experience surveying members (patients) by mail, telephone, and internet; and the ability to successfully identify, survey and interview prescribing physicians. KP databases have been used in numerous published studies for many years; all databases are readily linked over time via a unique medical record number; most data are available within days of clinical transactions. Because these databases have been in operation since 1995, a large population has been under observation for at least a portion of the past decade.

Each of the data sources listed in Table 1 represents one single database in each of our Northern and Southern California Regions, with uniform data entry standards. Both pharmacy and laboratory databases are directly archived from online clinical systems and are thus complete and accurate. Because KP is comprehensive and fully integrated, no element of care (e.g., mental health, chemical dependency, or chronic disease management) is "carved out" and therefore unavailable to researchers. All databases are complete for 10 years or more and therefore allow study of longer term outcomes.

Table 1 Basic KP Databases

	Comments
Membership Data	Monthly updates of membership status for each member, along with demographics (age, sex, residential address and zip code).
Hospital Discharges	KP captures hospital discharges from its 25 California hospitals and claims from outside hospitals (10% of admissions); primary discharge diagnosis (ICD-9), secondary diagnoses; multiple procedures; DRGs, admission status (elective/non-elective; and discharge status.
Outpatient Rx Data	Captures all prescriptions and refills dispensed; data include NDC codes, therapeutic classes, quantity, strength, daily dosage.
Outpatient Dx Data	Multiple ICD-9 diagnostic codes per outpatient visit; both primary and specialty; CPT-4 procedure codes
Laboratory Data	Complete outpatient and inpatient laboratory data for all hospitalizations at KP hospitals, including test results

Membership data are updated on a monthly basis; and contain demographic information (age, sex, residential address, and social security number) that allows automated statistical adjustment or matching, and linkage to U.S. census socio-economic data and to mortality data. Both regions (North and South) have geographically coded all member data to 2000 U.S. census block group data to provide proxy measures of socioeconomic status. Member addresses are updated at every clinic visit by clinic staff, which helps us maintain a very high contact and response rate to telephone and mailed surveys of KP members. Self-reported race/ethnicity information is recorded for all hospital discharges (see below) and is captured in member surveys. Together, these sources provide race/ethnicity information for more than 60% of members, with higher proportions among women and older patients. With the arrival of the new electronic medical record in 2006-08 (discussed below), race/ethnicity data will be routinely captured by the Health Plan and confirmed at outpatient visits in each region. With this capability we will eventually approach 100% capture of this data which we believe is essential to resolving health disparity issues.

Hospital discharge data. Most hospital discharges (90%) for KP members come from one of 25 KP-owned hospitals in California. At these hospitals, diagnoses (up to 15) and procedures (up to 11) are entered by coders who have been centrally trained and who use the identical coding software. The remaining 10% of discharges come from non-KP hospitals and are captured in a claims database with similar data elements. Many discharge diagnoses have been validated using medical record reviews.

Prescription data. Both inpatient and outpatient prescription data from more than 180 KP pharmacies are captured for nearly 100% of enrollees in both systems.

Approximately 95% of KP members have a pharmacy benefit. Moreover, KP pharmacies are located in or near all of our medical office buildings where outpatient services are provided. Convenient online and telephone refills are also heavily used. Thus, there is little incentive for members to fill prescriptions elsewhere. A recent survey among members with diabetes confirmed that only 3.3% reported obtaining any prescription outside of KP during the previous year. The small proportions of members without a drug benefit are often excluded from studies involving ascertainment of drug exposures. Prescription data include NDC codes and standard drug class codes (allowing for rapid selection of all drugs/strengths/ preparations within major therapeutic classes, such as oral hypoglycemics). Prescription databases also capture dates of dispensing, strength, daily prescription, and number dispensed (for calculating days supply, exposure over time, and adherence). Historically, prescription systems have not captured medications administered in ambulatory clinical settings, such as infused chemotherapeutic agents. However, all facilities in both KP California regions are in the process of implementing the pharmacy component of the new electronic medical record which will capture all such clinic-administered medications routinely.

Outpatient diagnosis data. Complete outpatient diagnosis data capture is a major advantage of KP databases. Diagnoses (from one to many) are recorded by clinicians at every ambulatory visit using optically scanned, specialty-specific encounter forms. Diagnoses are coded using an adapted ICD-9-CM coding system. In addition to identifying specific endpoints that may represent adverse events, these diagnoses are useful for assessing co-morbid conditions, either singly or in combination. Outpatient diagnoses are not likely to be as accurate as hospital discharge diagnoses. However, chart review validations of several outpatient diagnoses have been reported. In KP Northern California's diabetes registry, outpatient diagnoses captured more than 97% of all diabetic patients identified from any source, and only 9% of those identified by outpatient diagnoses were not also identified from at least one other source. Thus, outpatient diagnoses for diabetes appear to be both sensitive and specific. The outpatient database also captures procedures performed (e.g., retinal exam, sigmoidoscopy, pap smears) and clinical measurements such as blood pressure levels, body mass index, and smoking status. On January 1, 2004, both recent blood pressure values and smoking status were available in more than 92% of adult members in Northern California. These latter variables are useful in adjusting for case-mix differences (confounding) and also for disease severity differences.

Laboratory testing and results. Most laboratory testing in each region is performed in a single centralized, very high volume regional laboratory. Urgent testing is performed at hospital medical centers, but these results are also fed into the same database which supports both the clinical electronic medical record and archived databases used for research and quality assurance.

Many other research databases have been created within KP from these basic datasets. These include many registries (e.g., cancer, diabetes, HIV/AIDS, and total joint replacement). Some of these databases exist in only one region, but the code used to create each registry can be applied to the source data from the other regions.

The advantages of having such rich clinical data lie primarily in the ability to create detailed definitions of specific adverse drug events from electronic data. For example, it is a simple step to combine a discharge diagnosis of myocardial infarction (MI) with lab results showing cardiac enzymes to confirm or characterize diagnoses of MI; toxic hepatitis with repeated liver function test results; or neutropenia with repeated measures of white blood cell counts. Similarly, allergic reactions can be linked to prescriptions for oral corticosteroids to select more severe reactions.

Paper medical records. The ability to rapidly retrieve paper medical records dating back for more than 10 years is a unique advantage of integrated systems such as KP. After review and approval by a KP IRB, researchers may access these records for review. Research center staff work closely with medical records staff in KP facilities to retrieve both outpatient and inpatient records in full compliance with HIPAA requirements.

Fully computerized inpatient and outpatient medical record. KP is midway through the implementation of an entirely computerized inpatient and outpatient medical record, called "HealthConnect" across our entire program. (HealthConnect is the KP name for an Epic Systems electronic medical record.) Implementation has been completed in several of KP's smaller regions, is well underway in KP Southern California and has begun in Northern California. The pharmacy component is completed and it is anticipated that the entire record will be in full use throughout both regions by the end of 2008. This record includes prescription order entry in both inpatient and outpatient settings. It includes full text notes which can be scanned using text-processing to enhance the sensitivity and possibly the specificity of potential adverse events. The new record will routinely record self-reported race/ethnicity, as well as all vital signs. It will replace the need to retrieve paper records and allow analysts to simply scan records on screen for information that is not coded and archived in searchable databases.

Examples of Drug Safety Studies using KP Databases

Most of the recent studies that we have conducted have taken place within four separate research units that operate within the KP Northern and Southern California regions. These research units include the Division of Research (DOR), KP Northern California; the Research and Evaluation Department (R&E), KP Southern California; and Pharmacy Analytic Services (PAS) and Pharmacy Outcomes Research Group (PORG), both of which serve all of California. In the past two years, these four groups have combined to form the Kaiser Permanente California Pharmacoepidemiology Group (KPCPG). The KPCPG is a collaborative of KP researchers who have extensive experience conducting pharmacoepidemiologic studies, and a strong interest in collaboration with the FDA on studying possible adverse effects of FDA approved medications in the market, and experience collaborating with one another on a variety of studies. Following are several examples of important studies that we have conducted or will soon start using the resources I have described above.

1. Statin Use and rhabdomyolysis (muscle damage). In 2002, KP undertook a large-scale transition in statin use. Using a system-level intervention, more than 35,000 KP California members switched from other statin agents to lovastatin. By the end of the

transition, 80% of all statin users were on lovastatin (compared with 50% pre-intervention). Prior to the transition, KP clinicians had raised concerns regarding possible increases in rhabdomyolysis as a result. Researchers in PORG conducted a prevalence study over a one year period to identify the frequency with which elevations of serum creatine kinase (CK) were noted in persons taking a statin drug and to estimate the relative prevalence by statin preparation and dosage.[13] Lovastatin, even in high doses, was not associated with an increased risk of high elevations of CK compared with a moderate to high dose of simvastatin. Other clinical characteristics were also examined as possible predictors of high elevations of CK. Additional significant predictors of a high elevation of CK included elevated serum creatinine; use of a potentially interacting medication; male gender; and diabetes. The ability to go beyond simple detection of associations of drugs with adverse events to identify additional clinical characteristics that predispose some recipients to experience the adverse event given the exposure is a benefit of the very large size of our population and the richness of the automated clinical data.

2. Rofecoxib and the risk of acute myocardial infarction and sudden cardiac death. Concern that rofecoxib may increase the risk for serious cardiovascular events was first raised in a post-marketing clinical trial of its relative effectiveness.[9] Members of PORG, in collaboration with FDA, conducted a large case-control study nested in a cohort of over 1.3 million users of COX-2 selective and non-selective nonsteroidal anti-inflammatory agents. They found that rofecoxib increases the risk of serious coronary heart disease. This study, together with data from another clinical trial using rofecoxib to prevent colorectal adenomas, led to withdrawal of the agent by its manufacturer in October 2004.[11,12]

3. Topical tacrolimus/pimecrolimus and the risk of cancer. In March 2005 FDA issued an advisory to doctors urging caution in prescribing topical tacrolimus or pimecrolimus because of an increased risk of cancer. The concern was based solely on information from animal studies, case reports in a small number of patients and the pharmacology of the drugs. At KP, we have the capability of merging our pharmacy database with our cancer registry thus identifying patients who have been prescribed these two drugs and diagnosed with cancer. PORG compared the rate of different cancers among patients with eczema or atopic dermatitis who have or have not been exposed to topical tacrolimus or pimecrolimus. The preliminary result of the study included close to 1 million California members with 2.5 million person-years of follow up time. KP researchers did not find an increase in overall cancer rates but there was an increase in cutaneous T cell lymphoma among drug users. Since KP is integrated, our researchers were able to examine the electronic and paper medical records of some of these cases of cutaneous T cell lymphoma. These allowed us to confirm these cases and exclude those that the physicians suspected of having cancer prior to receiving the drugs. KP researchers concluded that there was no increased risk of cancers or T cell lymphoma following exposure to either topical tacrolimus or topical pimecrolimus.

4. Attention-Deficit/Hyperactivity Disorder (ADHD) medications and the risk of serious cardiovascular disease. Funded by the FDA, this study is currently underway and is a collaborative effort involving KPCPG, Vanderbilt University, United HealthCare, and the HMO Research Network. According to a summary from the FDA's Adverse Events Reporting System; cardiac arrest, myocardial infarction, and death are among the top 50 most commonly reported adverse events for ADHD medications. Of all deaths, a substantial number were cardiac deaths, associated

either with sudden collapse or with symptoms of MI. Deaths were reported in both children and adults. This retrospective cohort study will analyze whether these medications confer an increased risk for cardiovascular disease in children and adults.

5. Aromatase inhibitors and the risk of hip fracture among breast cancer survivors. In 2004, the American Society for Clinical Oncology recommended aromatase inhibitors as a first line adjuvant therapy for postmenopausal, hormone receptor-positive breast cancer. The Society noted, however, that the long-term consequences of aromatase inhibitor therapy, specifically osteoporosis, are not well characterized. Clinical trial results suggest that an increased frequency of hip fractures accompanies aromatase inhibitor use in the prevention of breast cancer recurrence. However, this association has not been quantified in a large population of breast cancer survivors that is representative of all women treated in clinical settings. Rather it has been limited to women eligible and willing to participate in a treatment trial. The goal of this study, conducted by PORG in collaboration with researchers from Wake Forest Medical Center and the University of Michigan, is to estimate the risk of hip fracture hospitalization among approximately 9,000 KP breast cancer survivors receiving aromatase inhibitors (anastrozole, letrozole, exemestane) compared to those receiving tamoxifen therapy.

6. Atypical Antipsychotics and onset of diabetes. Another safety study in the planning stage is to assess the incidence and comparative rates of newly diagnosed diabetes and other indicators of metabolic syndrome in patients receiving different atypical antipsychotic agents. The use of atypical antipsychotic drugs has been associated with the development of a metabolic syndrome, whose core features include insulin resistance, type 2 diabetes, dyslipidemia, hypertension, and abdominal obesity. The integrated KP databases--including over 6 million enrolled members, full laboratory results and detailed coded data on outpatient diagnoses--is the ideal setting for this study. KP researchers will assess the relative risk of drug-induced new onset diabetes as differential effects on plasma lipids such as LDL-cholesterol, HDL-cholesterol and triglycerides. Results from this study will provide clinicians with added information to help guide their choices of atypical antipsychotics for individual patients

Concluding Remarks

These are just a few examples of what is possible in terms of using existing data, and the future availability of complete clinical data capture with electronic medical record systems like Kaiser Permanente's HealthConnect, to enhance significantly the ability of researchers to more quickly identify problems. The experiences we are gathering today will help shape our ability to take full advantage of the new digital health care environment, to improve the safety of drug therapy and to understand more fully the risk-benefit profile that specific drugs offer to individual patients.

If we are to take full advantage of this research capability to substantially increase the safety of prescription drug use in this country we need *time* to find safety problems before too many people are exposed to unproven new drugs. The aggressive marketing of new drugs both before and after FDA approval--including drugs that are only marginal improvements over existing therapies--does not allow sufficient time for this to happen. A solid case can be made for policies that would make drugs available in a more well-organized and thoughtful manner. Certainly this

committee will have a great deal to say about that, and I encourage you to explore ways to make sure that drugs not only come to market in a timely manner, but also that the data collection that follows release and marketing is organized in a manner that avoids exposing patients to unnecessary risk.

We would also ask that you consider making additional resources available to the FDA and to the research community to pursue answers to questions raised about particular drugs and conduct broad post-market surveillance activities.

Finally, I hope that it is clear from my testimony that the expanded use of comprehensive, clinically based electronic health records is vital to improving our research capabilities. It will be essential that the public and private sectors cooperate to ensure that the appropriate data elements are widely used and the ability to match appropriate clinical, demographic, encounter and related data elements across providers is built in to these systems.

Thank you again for the opportunity to testify today. I look forward to your questions.

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*Summarized from an RFP submitted to FDA for post-marketing pharmacosurveillance written by Dr Joe Selby on behalf of KPCPG

Mr. PALLONE. Thank you, Doctor. Dr. Powers.

STATEMENT OF JOHN POWERS, M.D. ASSISTANT PROFESSOR OF MEDICINE, THE GEORGE WASHINGTON UNIVERSITY SCHOOL OF MEDICINE, AND UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE

Dr. POWERS. Thank you, Mr. Chairman and members of the committee. My name is John Powers, and I am a physician scientist who worked at the Food and Drug Administration for the last 8 years. My background is that of a practicing clinician and academic investigator and researcher, a scientist in the field of drug development, a consultant for several drug sponsors, and most importantly, I have been a patient myself. I would like to thank you for the opportunity to discuss with you today my perspective on the issues of evaluating the risks and benefits of medical intervention.

The Institute of Medicine report on drug safety points out that the current reauthorization of the Prescription Drug User Fee Act is a golden opportunity to address long overdue improvements needed in our system of evaluating drug safety. The GAO report points out that there have been at least five separate reports since 1971 related to these issues. Therefore PDUFA should not be reauthorized without simultaneously addressing the important public health issues related to drug safety that have persisted for some time.

Previous drug legislation addressed the issues of pre-approval safety in 1938 and pre-approval effectiveness in 1962. But it is now clear that we need more focus on continuously evaluating drugs even after approval.

For instance, the example of the inevitable emergence of antibiotic resistance points out how the assessment of both safety and effectiveness of drugs can change over time. The standard we should use to judge proposed changes in drug safety should be would these changes prevent another safety episode like Vioxx of Ketek? Tying pre-approval review that brings medical interventions to patients and appropriate post-approval evaluations of those same interventions are not mutually exclusive goals, and we can do both.

I would like to divide the issues related to addressing drug safety into three categories. First, inputs of resources in authority into FDA. Second, internal use of science resources and processes inside FDA. And third, outputs of decisions and communications with the public from FDA.

In terms of inputs into FDA, Congress should authorize adequate funding for general appropriations, and any PDUFA fees should have no strings attached, and their use should not be negotiated with regulatory industry. FDA needs the authority to require post-approval studies, to mandate labeling changes, and to assess simple monetary penalties for not fulfilling risk management activities.

The legislation proposed by Mr. Markey and Mr. Waxman is a start in this direction by providing more meaningful penalties. FDA needs access to modern databases and active surveillance to more efficiently gather information on drug use and potential adverse events.

Any organization is only as strong as the people who work there, so FDA needs to hire adequately trained staff and ensure the staff remain engaged as a part of the scientific community. This leads to issues involving science and process inside of FDA. FDA scientists should be free to participate as members of the scientific community by having the right to publish and share their information and participate in scientific meetings.

There needs to be a culture of professionalism at FDA. And if, on rare occasions, after attempting to reach internal agreement, FDA staffers need to seek help outside of FDA in order to protect the public's health, there needs to be enhanced whistle-blower protections, such as those outlined in Mr. Markey's Swift Approval Full Evaluation Act.

There also needs to be accountability for FDA staff who attempt to retaliate against their colleagues or who do not uphold the laws and regulations. For instance, in cases where drugs have been knowingly approved without substantial evidence of effectiveness.

Any system should have checks and balances, and the Office of New Drugs and the Office of Surveillance and Epidemiology should have joint decision-making authority regarding post-approval decisions. FDA needs to define what they mean by best use of science and define the criteria used for making risk/benefit decisions in general.

In terms of outputs from the FDA, we need transparency of decision making in the form of summary bases of approval published on the FDA Web site in a timely fashion, which explain the scientific rationale for regulatory decisions. This would be helpful for both regulated industry and for patients. All clinical trials and their results should be included in a registry.

It is FDA's job to communicate with the public, and FDA needs the resources to evaluate the effectiveness of all of the methodologies used to try to accomplish this goal, as it is well known that changes in labeling alone have little effect on prescribing behavior.

The IOM report reinforces that now is the time to address sorely needed improvements in evaluating drug safety. Congress should include provisions for strengthening drug safety in any reauthorization of PDUFA. We can address issues in evaluating drug safety in an efficient way without hindering access to important medical advances for patients.

Making these changes today will help us to avoid another Vioxx or Ketek tomorrow. Congress can help FDA start down the road of being the foremost authority on pharmacoepidemiology, to help them work closely with the scientific community, and to develop scientifically-based approaches to evaluating the balance of risk and benefits for drugs.

This will help FDA achieve its stated mission of protecting and advancing the public health. Most FDA staffers are incredibly hard workers and courageous public health servants. Please give them the tools they need to do their jobs for all of us. Thank you.

[The prepared statement of Dr. Powers follows:]

STATEMENT OF JOHN H. POWERS, M.D.

Good morning Mr. Chairman and members of the committee. My name is John Powers. I am a physician-scientist who worked at the Food and Drug Administra-

tion for the last 8 years. My background is that of a clinician in internal medicine and infectious diseases, an investigator and researcher in clinical trials, a scientist in the field of drug development, and a consultant for several drug sponsors. Perhaps most importantly, I have been a patient myself. I would like thank you for the opportunity to discuss with you today my perspective on the issues of evaluating the risks and benefits of medical interventions.

As the Institute of Medicine report on drug safety points out, the current reauthorization of the Prescription Drug User Fee Act is a golden opportunity to address long-overdue improvements with drug safety in order to adequately protect the public's health. PDUFA should not be reauthorized without simultaneously addressing the important public health issues related to drug safety. The standard we should use to judge proposed changes to the evaluation of drug safety should be: Would these changes prevent another drug safety episode like Vioxx or Ketek? Bringing medical interventions to patients in a timely way and appropriate post-approval evaluations of those same interventions are not mutually exclusive goals, and addressing post-approval drug safety need not slow bringing new medications to patients. Indeed, the FDA Critical Path initiative points out that better tools for pre-approval evaluation of potential safety issues may allow more efficient drug development, earlier cessation of drug development programs of drugs with toxicities before spending precious resources, and more focused evaluation of drug toxicities post-approval.

The passage of the Food, Drug and Cosmetic Act (FD&C) in 1938 shifted the burden of the evaluation of pre-approval safety of drugs from the government to drug sponsors. From that time forward there was no assumption that a drug was safe, and sponsors had to provide evidence of the potential adverse events associated with drug use. This reflected a notion that is clear today; no drug is completely safe in that all drugs are associated with some adverse events. In 1962, Congress amended the FD&C Act to require substantial evidence of effectiveness based on adequate and well-controlled trials, codifying the logic that there must be evidence of benefit in order to justify any risks of drugs, no matter how rare.

Both these provisions focused on the pre-approval evaluation of medical interventions, which was appropriate for that time. However, it is now clear that we need to focus on the entire life-cycle of medicines with a greater focus on post-approval evaluations. This is eminently sensible as we cannot learn all we need to know about medical interventions given the limited number and types of patients and the short time span in which drugs are studied pre-approval. The vast majority the life-cycle of a drug is spent post-approval, and it follows we can learn much about a drug during this time. FDA must play a crucial role in continuing to evaluate drugs once they are approved.

The need for regulation is two fold: first, regulation is needed when market forces tend to guide businesses in a way that may be contrary to public interest, and second, regulation provides a uniform standard for public health and consistency and fairness for the regulated industry. In regards to the first point, there is little incentive for drug sponsors to rigorously evaluate potential safety issues with a drug once it is approved since from a business perspective this evaluation has the potential to decrease sales. This is in contrast to providing evidence of drug effectiveness prior to approval which is necessary both for FDA approval for marketing and to convince clinicians to use the drug. Many drug sponsors certainly do include protecting the public's health in their decision making. But as James Madison stated in the Federalist #51 in 1788, if all men were angels no government would be necessary. Even one sponsor who decides that profits trump public health is one too many and it is the FDA's job to ensure all sponsors are held to the same standard. This relates to the second point, which is that FDA is supposed to ensure a scientifically based and consistent standard of public health both for the sake of the public health, and out of fairness to drug sponsors so that every sponsor is subject to the same rules. This allows less uncertainty in drug development, and allows sponsors to plan their studies accordingly. The only way to ensure both protecting and advancing the public health and fairness to drug sponsors is to base laws and regulation upon the best science. Since science changes over time as we learn new things, regulations need to adapt as well. The prior focus on pre-approval evaluations is still needed, but we now need to focus our attention of post-approval evaluations as well.

One can view the issues related to addressing drug safety as divided into three categories: inputs of resources and authority into FDA, internal use of resources, science and functioning inside FDA, and outputs of decisions and communications with the public from FDA.

I. Inputs into FDA

FDA staff need the resources in terms of funding, manpower, knowledge, data and authority to do its job properly.

Congress should authorize adequate funding for FDA from general appropriations and PDUFA fees should have "no strings attached" and not be negotiated with regulated industry: FDA has been severely under-funded for some time, even to do the job it already has to do. Indeed, the original intent of PDUFA in 1992 was to bring greater funding to FDA to provide it the resources it needed at that time. To address the larger issues of post-approval evaluations of drugs it will need greater funding. It seems logical that regulated industry should pay for a fee for licensing of drugs to defray the costs to the government, similar to how drivers pay a fee for their drivers' license of doctors pay a fee to State medical boards for a license to practice medicine. However, drivers and doctors do not negotiate the uses to which those fees are put with Division of Motor Vehicles or the State Medical Board. In addition to the obvious appearance of conflict of interest of allowing the regulated to help decide where the regulator appropriates funds, the long time frame between PDUFA negotiations—done only once every 5 years—does not allow FDA to adapt and shift resources to where they are most needed. Again, there is a need for regulation when there is no incentive for the regulated to address issues of public health, and previous negotiations of PDUFA in which FDA was barred from applying fees to post-approval safety evaluations are evidence of a desire by some to avoid performing these evaluations.

FDA needs adequate authority to ensure the public health including ability to assess sufficiently stringent civil monetary penalties for non-adherence and sufficient authority to ensure device effectiveness—FDA needs the authority to require post-approval studies and ensure sponsors complete those studies. As noted previously, there is an obvious incentive for drug sponsors to submit data in support of drug effectiveness. Since there is less incentive to perform post-approval studies, FDA needs the ability to require studies and impose meaningful penalties on drug sponsors who do not fulfill their stated commitments. The Enhancing Drug Safety and Innovation Act (H.R. 1561) is a start in this direction by providing for more meaningful penalties beyond those that sponsors could just write off as the cost of doing business. Penalties need to be appropriate in order to provide an incentive to comply. In addition, the current legally mandated standards for effectiveness of devices are quite different for those from drugs. It is not clear from a scientific point of view why this should be so, as patients who receive devices should receive the same protection under the law as those who receive drugs. Recent approvals of some devices have left outstanding questions regarding their effectiveness, such as the vagal nerve stimulator for depression. This seems to contradict the basic principle that there needs to be substantial evidence of effectiveness in order to justify the risks of any intervention. Congress should address this by changing the law to hold devices to the same standard of substantial evidence of effectiveness from adequate and well controlled trials as for drugs.

FDA needs adequate data upon which to base decisions—The use of modern databases to more efficiently gather information on drug use and potential adverse events is desperately needed. FDA cannot rely on the good graces of busy clinicians for spontaneous reports of adverse events. Many medical schools do not teach their trainees about the need to report adverse events, so there is a need for education as well. FDA always needs to stay in touch with practicing clinicians, but they cannot be the only source of information in evaluating medical interventions post-approval. In addition, for reasons discussed previously drug sponsors cannot be the sole source of information. There is little incentive for them to report adverse events and there are recent unfortunate examples in which important information was withheld from FDA. If FDA had independent sources of information this would be less of a concern.

FDA needs to hire adequately trained staff—It is important that FDA hire, train and keep staff who have a background and training in drug development and evaluation. It is sad to say that many in academic medicine view a career at FDA for their trainees as "a waste of time" and "unscientific". FDA needs to be on the same scientific par as the National Institutes of Health and the Centers for Disease Control and Prevention in terms of scientific reputation and in terms of appropriately applying science. The only way to accomplish this goal is if the scientific community has positive interactions with FDA staff, instead of the current "black box" that clinicians see as the current FDA.

FDA needs close contact with the scientific community—FDA has to have a symbiotic relationship with clinicians and scientists. As science is ever-changing, FDA staff need to keep abreast of the latest scientific developments. In addition, FDA

staff have much to teach the scientific community about clinical trials and the pharmacoepidemiology, and much of the view that FDA is "unscientific" comes from a lack of understanding of the scientific principles upon which appropriate drug evaluation is based. This means that FDA staff need to be able to interact with scientist in their fields, an issue I will address in terms of outputs from FDA as well.

II. Science and Process Inside FDA

FDA has become too focused on "process" to the exclusion of the reason for why process is needed. The process as FDA should serve good science which in turn protects and advances the public health. Science should not serve process. Appropriate processes are needed in order to drug sponsors to submit data and for FDA staff to review this data in an orderly way. However, on the Center for Drug Evaluation and Research guidance page there are 53 guidances under the heading of "process" and 3 under the heading of "drug safety". Clearly this balance seems tilted in the wrong direction. FDA managers needs to treat the scientists and review staff with professionalism and the basis for decision making needs to be good scientific principles

FDA managers need to treat staff with professionalism—Science is based on the scientific method, and as such, any one who uses this method, from the medical student to the senior attending, can make equally valid analyses and draw equally valid conclusions. As with school teachers, if most of their class fails the examination, they must take part of the blame. If FDA managers believe their staff is not using appropriate scientific analyses, then it is incumbent on these managers to train staff in these same principles and provide mentoring for them and career development paths. It is inappropriate and unprofessional to characterize scientists who raise scientific issues as "disgruntled" or to characterize a scientist work as "junk science". FDA managers need to realize that there are substantial issues with the relationships between managers are staff at FDA that need to be addressed. A Union of Concerned Scientists poll of FDA staff showed that 44 percent of FDA scientists did not respect their managers' integrity. A substantial shift in culture at FDA is needed, and this can be accomplished by making FDA place where people who follow the scientific method and who treat their peers with respect want to work and those who choose not to behave professionally don't want to work

Joint authority of Office of New Drug and Office of Surveillance and Epidemiology regarding post-approval decision making. It is part of the scientific method that data, analysis and conclusions undergo peer review and re-analysis by others to confirm the conclusions of a given set of scientists. Also, it is only human nature that when one makes an important decision that may affect the lives of thousands or million of persons it is very disheartening to learn that decision may have resulted in people being harmed. However, it is also part of science that we learn more as more evidence accumulates. Lastly, systems function best when there are checks and balances and no one person or group of persons exerts absolute authority. The framers of the Constitution set up a bicameral legislature and three branches of government for exactly this purpose. For all these reasons there needs to be joint decision making authority between the Office that approves new drugs (the Office of New Drugs) and the Office responsible for evaluating drugs after approval (the Office of Surveillance and Epidemiology). The Enhancing Drug Safety and Innovation act could be strengthened by including provisions for this joint authority.

Accountability for decision making and behavior at FDA and increase "whistleblower" protections -There needs to be accountability for FDA managers who treat staff unprofessionally, both from within FDA by senior managers and from oversight from Congress to ensure that accountability takes place. Increased transparency of the operations at FDA would discourage some from inappropriate behavior, and all of FDA would benefit from changing the perception held by many clinicians, academics and those in industry that FDA is a "black box" in which operations, decision making and the scientific reasoning behind decision making seem unclear. There is no blind acceptance of data in science, and statements that "FDA cannot be second-guessed" do not take into account that "second-guessing" (also called peer review and confirmation of evidence) is part of science. One of the basic premises of the scientific method is we can never be sure we are correct, but we can always be proven wrong, so one needs to keep an open mind at all times. No one questions that FDA managers have the authority to render decisions, but with the authority comes responsibility. There is no such thing as the FDA, as FDA is made of up individuals. It would be best if no staff person at FDA ever has to "blow a whistle" on inappropriate use of science or failure to protect the public's health, but should this be necessary, FDA staff need to know they will not be risking their livelihood to protect

patients. Therefore there needs to be increased whistle-blower protections such as those in the legislation proposed in the Swift Approval Full Evaluation act.

Best Use of Science and Consistency of Decision Making within FDA and publication of guidance on risk-benefit analysis—One of the major complaints of drugs sponsors is that they receive inconsistent advice from FDA. While in some cases advice can and should change as science advances during the course of drug development program, some sponsors feel that they do not receive consistent scientifically-based advice from Division to Division within FDA across similar drug development plans in different therapeutic areas. This would seem at odds with using appropriate scientific methods to make decisions. FDA needs to train staff on the scientific and legal bases for drug evaluation, especially in that there are legally mandated standards for drug effectiveness that must be followed in order to justify the potential adverse events of drugs. FDA needs to formulate guidance which explains the scientific decision making process of balancing risks and benefits. While there needs to be some flexibility to accommodate individual cases, there are some basic principles which would apply to all situations, such as evaluating the frequency, severity and seriousness of adverse events weighed against the nature and magnitude of the benefits of a medical intervention. FDA reviews need to explain the scientific as well as legal basis for decision making and conclusions so that sponsors, clinicians and the public can understand the scientifically reasoning behind a decision. FDA reviews include a tremendous amount of data and analysis but is it not always clear how this data is synthesized into an overall decision.

III. Outputs from FDA

FDA serves the public and therefore needs to communicate with the scientific community, clinicians and patients as well as drug sponsors.

Transparency of decision making and reviews at FDA—The Belmont Report in 1979 on the protection of subjects in human research pointed out that research is the pursuit of generalizable knowledge. For research to be ethical the knowledge obtained must be generalizable in order to justify exposing subjects to the risk of the research. If research is not generalized, that is, shared with others in the scientific community then it is inherently unethical. Therefore it is incumbent upon FDA and drug sponsors to share the information from all clinical trials. A registry that includes a listing of all clinical trials including the results of these trials would allow knowledge to be generalized. The Enhancing Drug Safety and Innovation Act includes such a provision. It is important that data from earlier phase trials be included in such registries and databases as these earlier phase trials often form the basis for evaluation of further adverse events post-approval. In addition the results of these trials, not merely that fact that they are ongoing or completed, need to be included in any database in order for the results to be generalizable. FDA reviews should be published on the FDA website within a reasonable period of time (no longer than a few weeks) in order for the scientific community to evaluate the basis for FDA decision making. This form of peer review is part of the scientific process.

FDA staff should have a right to publish and participate in scientific meetings—As noted previously, FDA reviewers need to keep current with the science in their field. This means FDA staffers need to share their knowledge with those outside FDA as well as gaining knowledge themselves from scientists outside FDA. FDA reviewers need to be able to share their analyses with the scientific community and the need to FDA managers to "make one decision" should not bar a scientific discussion among the scientific community. The Supreme Court "make one decision" and yet members of the Court still publish a minority as well as a majority explanation of their findings. Therefore, FDA should publish a Summary Basis of Approval (SBA) for each medical intervention which would include a discussion of any and all scientific differences during the review process and an explanation and scientific reasoning for the final conclusions.

The IOM report tells us that now is the time to address the important issues in evaluating drug safety that have needed to be addressed for some time. In order to address this urgent public health issue, we need to act now. Congress should include provisions for strengthening the evaluation of drug safety in any reauthorization of PDUFA. A recent Harris poll showed that the public is losing confidence in FDA, and the only way to restore that confidence is by action, not merely by words or reshuffling of the structure of FDA and without new resources and authority. We can address the important issues in evaluating drug safety in an efficient way without slowing bringing important medical advances to patients. Safety and efficiency and not mutually exclusive goals and more focus on post-approval activities need not slow pre-approval evaluations. However, we need to learn from recent events and take action today to avoid another Vioxx or Ketek tomorrow. Congress can help

FDA start down the road to being the foremost authorities on pharmacoepidemiology, to work closely with the scientific community to gather data and to develop new methods and analyses, to come up with cogent scientifically based approaches to evaluating the balance of risks and benefits of drugs, and help FDA achieve its stated mission of protecting and advancing the public health. Most FDA staffers are courageous public health servants. Please give them the tools they need to do their jobs for all of us.

Mr. PALLONE. Thank you. And we will take questions of the panel now. Thank all of you again for being here. I am just going to recognize myself for 5 minutes for some questions, and I wanted to ask a couple questions of Ms. Thompson.

First of all, let me thank you for all the good work you do with the Elizabeth Glaser Pediatric AIDS Foundation. I am familiar with it, and I really know that you do a great job. But I found your testimony interesting because you suggest that the goals of a strong and robust drug safety system and at the same time, innovative medicines are not necessarily mutually exclusive, that you could possibly do both. And I am wondering if you could elaborate more on why you think that doesn't have to be an either/or scenario? In other words, if we were to pass drug safety legislation that built upon what is already included in the PDUFA IV proposal, that included stronger monitoring and enforcement provisions—in other words, like if we did what Mr. Waxman and Mr. Markey have included—do you think that would kill innovation? Or would we still be able to be innovative, so to speak?

Ms. THOMPSON. Well, I think we strongly believe that it won't, in fact, kill innovation. What the IOM has proposed and what, I think, has been picked up both in the Waxman-Markey bill and the Kennedy-Enzi bill is to address this new paradigm of looking at safety concerns throughout the life cycle of the drug. So it is really taking the FDA back, in some senses, to its roots under the original 1938 statute, which was all about safety. Of course, efficacy wasn't added until 1962.

So by providing FDA the resources that it needs to maintain its scientific excellence, the resources that it needs to integrate more fully safety concerns both into the drug review process and into the post-market surveillance process, I think you have got the perfect recipe for enabling innovation to continue and, in fact, supporting it because one of the areas that has suffered under PDUFA is the FDA science base.

And FDA, in order to support the innovation that is coming out from industry, needs to be the leader in terms of regulatory science and in terms of advancing the tools and techniques that are going to support regulatory discovery and how that discovery gets translated into new therapies.

Mr. PALLONE. Thank you. In your testimony, you call for giving FDA authority to require testing for off-label uses of drugs. But if Congress granted FDA such authority, how would that match up with the Pediatric Incentive Program? How exactly would those two programs work together? Would granting such authority obviate the need for the incentive program? If you would explain.

Ms. THOMPSON. Well, the answer is no, it would not obviate the need, but we begin with the position that three-quarters of the prescriptions that are written for children are written off label. And

the Pediatric Incentive Program, the program you referred to, BPCA, Best Pharmaceuticals for Children Act, provides a voluntary mechanism where FDA can go out and, if the drug is still on patent, it can recommend to a manufacturer that the manufacturer conduct certain studies to determine effectiveness and/or safety in children.

But that only applies on a voluntary basis. Obviously under the stick part of that equation, the pharmaceutical research side, that legislation for the most part applies only to new drugs. And there is a very high standard that FDA has to meet to require studies now, very high safety finding or danger finding that the FDA has to make.

So providing new authorities in combination with the existing carrot-and-stick approach under pediatrics is really essential if the FDA is going to be able to identify safety and effectiveness for children.

Mr. PALLONE. Thank you. I am just going to try to get in a couple questions here to Ms. Van Syckel. Thanks again for being here. But in your testimony, you don't specifically call for the repeal of the user fee system. In fact, you suggest that it should be expanded, but you call for it to be decoupled from obligations made to the industry. Would you just comment further on that? And then I am going to ask you also a second question. You have been very vocal about improving communications about medications to patients and providers, and you have focused on the availability of the distribution of med guides. Is there something that you think Congress could do to improve communications about medication risks through changes to the med guide system? So second, the med guides, and third this whole idea of decoupling the user fee system.

Ms. VAN SYCKEL. OK, let us start with the med guides first.

Mr. PALLONE. OK.

Ms. SYCKEL. First we have a bill, S. 2364, in New Jersey that is sponsored by Senator Codey and Senator Lance. We have got two good guys there. And what we are trying to do is these medication guides, we don't want to find them, if we get them, in the bottom of a pharmacy bag. So what we would like is to have parental informed consent. Look at the med guide with the doctor, go over the med guide, don't just put it in the bottom. I took this off the Internet. It is that simple. Doctors can do that.

And I asked Assemblyman Conaway, because we had discussed this issued. And I said Doctor, have you seen the med guide? And he said yes, and I guess he assumed he had. And I said well, could you please tell me what to look for? And he couldn't tell me, and this is a doctor within New Jersey on the assembly.

And I think it is important because everybody is so concerned about the thoughts of suicide. There is a lot more of side effects than just the thoughts of suicide, and those are newer, worse irritability, acting aggressive, being angry or violent, and acting on dangerous impulses. And I will give you an example from New Jersey. There was a young teenager who was an honor roll student, participated in peer groups. He was over-medicated, and he brought a cache of weapons to school, loaded guns, to even the point that the father, the parents didn't even know where he got the guns.

So violence issue with the anti-depressants has become very—is something that we should all be concerned about, and I was so concerned that I attended a White House conference on school violence and school safety. And I did have an opportunity to speak to Attorney General Alberto Gonzales concerning this issue, and I have even spoken to Mr. Ferguson because I saw how my daughter attacked three police officers, assaulted her brother. I see how violent the children become. And the Attorney General asked Secretary Leavitt, sent him a letter back in October to look at the violence issue concerning the antidepressants.

So if parents don't have this med guide, and I think it is very insulting for the FDA to say that there are some outsiders who should determine what parents need to know. This is what we need to know so if we make a decision to give them an antidepressant, we can monitor them. The doctor can't do it. The school district can't do it. It is up to the parents, and we need this vital information.

I guess I was kind of being diplomatic with PDUFA. If it were up to me in the great world, I would like to have it repealed. But it is not the perfect world, and I believe we need to focus more on an independent office of drug safety. I am trying to be diplomatic but I sometimes can't. I truly believe we need an independent office of drug safety. I agree with Senator Grassley and Senator Dodd on this issue. They have been at this issue for 4 years. They are knowledgeable.

Mr. PALLONE. OK, thank you so much. Mr. Deal.

Mr. DEAL. Mr. Theriault, I share your concern for counterfeit drugs. In a previous hearing that we had where the issue came up about adverse events, a questions was asked as to whether or not there was any way, with our current information, to distinguish adverse events that might have been caused by counterfeit drugs as opposed to brand-name drugs. And the general answer was no, there was not. Is there anything that we should to do to try to deal with that particular issue? And are there things that we might do that would—might have adverse consequences, thinking we were doing the right thing?

Mr. THERIAULT. The adverse event reporting issue is something that I think is difficult, and I am not sure how you can differentiate between adverse events that are caused by counterfeits as opposed to legitimate medicine. From our point of view, the safety issue is addressable on a number of fronts. I think that stopping these personal use amounts of prescription medicines that come into the country, via the mail services and that sort of thing, is almost a no-brainer.

We conducted a study about 2 years ago, and at the New York City mail facility alone, there were over 40,000 packages a day coming into that one mail facility that were identified as unapproved pharmaceuticals. Tightening the supply chain, requiring pedigrees, enforcing the pedigree aspect of PPNA. I think you can't regulate the Internet, but I think you can regulate the flow of products that are ordered on the Internet.

Mr. DEAL. Could you give us some idea what proportion you think are coming in from outside of the country versus counterfeiters who are operating within our own country?

Mr. THERIAULT. In the last 10 years that I have been at Pfizer, we have had probably the most aggressive anti-counterfeiting program in the industry. And I can't recall one counterfeiting manufacturing operation that we found in the United States. I would say the very, very high percentage of counterfeits in the 1990s comes from outside the United States. And that is why, when we address importation and issues like that, I think that unless we deal with the drugs coming in from outside the United States we are going to have a problem.

Mr. DEAL. Your written testimony indicates one particular, I think it was an Internet pharmacies supposedly in Canada. How big a problem is Internet pharmacy in this overall problem of counterfeiting?

Mr. THERIAULT. Well, I think it is a huge problem. And to your earlier point, the woman who died in Canada, I think, was a U.S. citizen residing in British Columbia. As I understand the facts, the medicine she received came in an unmarked vial. There was no label, no safety information. There was very little possibility to determine where she bought those, and the Internet pharmacy that sell those things are up and down in a matter of days.

So I think if you buy prescription drugs on the Internet, you are taking about a 50 percent chance of getting either counterfeit or unapproved generic medicines.

Mr. DEAL. And I suppose you would support increasing the penalties for the counterfeiting of drugs, would you not?

Mr. THERIAULT. Yes, sir, I would. I think Congressman Rogers' bill is an excellent step in that direction.

Mr. DEAL. OK, I would like to briefly explore the procedures that are embodied at FDA now. I believe we refer to them as the critical path. Dr. Powers, since you have worked there, would you briefly comment on that initiative and whether you think it is appropriate?

Dr. POWERS. Sure, the critical path was initiated in March 2004, which is an attempt for FDA to partner with folks outside the FDA, both academics and people in practice, to try to develop tools that would more efficiently help drug development, both in terms of measuring safety and effectiveness. It is a great idea, but it is one in which FDA is left in the position of having to suggest things to people outside the agency and really doesn't have funding at this point to be able to accomplish those things.

So they published several, including one last week on generic drugs, saying here are some great things we would like to know the answers to, but are left without the resources to be able to do that in a lot of cases.

For instance, let us take the issue of biomarkers. The way for us to explore whether those biomarkers are helpful in selecting which patients may benefit or which patients are at risk would mean looking at studies to see whether those biomarkers make any sense or not. And right now, FDA is left in the position of suggesting saying wouldn't this be a good idea.

Mr. DEAL. Money would help.

Dr. POWERS. It sure would.

Mr. DEAL. Thank you.

Mr. PALLONE. Mr. Ferguson.

Mr. FERGUSON. Thank you, Mr. Chairman. Thanks to all of our witnesses on our second panel. As most or some of you know, I spent my time in the first panel talking about medication guides. It is something I have spent a great deal of time on, and Lisa and I have actually worked on the issue a lot together.

Lisa, we have heard your testimony today. Of course, I am very familiar with your own family's story. It is important that you continue to share that with folks, including in this setting, so people can just understand one family's situation and ordeal. And you had said before you represent kind of families in New Jersey, but you are not an official organization or group.

Ms. VAN SYCKEL. No, I am a mom.

Mr. FERGUSON. You are a mom. You are a parent like I am and so many of us are, trying to make sure you are taking care of your child and having information to take care of Michelle——

Ms. VAN SYCKEL. And Chris who is down in Florida.

Mr. FERGUSON. Yes. Now, with regard to the medication guides, you know that in 2004, we had our Oversight and Investigation Subcommittee hearings and investigations into this particular issue. And subsequent to that, these medications, SSRIs, who are prescribed for kids now are accompanied by or supposed to be accompanied by medication guides. That was after your family situation.

Ms. VAN SYCKEL. That is right.

Mr. FERGUSON. If you can hypothesize, I guess, or——

Ms. VAN SYCKEL. Finding out that the med guides weren't being distributed?

Mr. FERGUSON. Well, actually how would that have affected your own family situation? If you had been presented with a med guide when you filled that prescription for your daughter—I mean it is tough in hindsight to be able to go back and figure out what you would have done but——

Ms. VAN SYCKEL. And I don't believe I, at that time, would have known what to do because Michelle really didn't have depression or anorexia. It turned out she had Lyme disease, so we were desperate to help her. So would I have done this? I don't know. I may have, but armed with this information at least, I could have prevented the self-mutilation, the scars that are on her body today.

We have a young girl who came to your office, and no one is immune to the side effects of the antidepressants, and this young girl, both of her parents work for the pharmaceutical industry. And if you look at her arms, do those look like little scratches to you? Cutting the word "die" onto the inside of your arm? Is that an acceptable side effect? I don't think so.

Mr. FERGUSON. Now, you——

Ms. VAN SYCKEL. But it is not here.

Mr. FERGUSON. You obviously are in touch with and work with other families who have had similar situations that we have met with.

Ms. VAN SYCKEL. They call me desperately seeking answers because they said my doctor told me it was safe and not to listen to the stories in the media, that they are parents that are—they are actually labeling parents like me.

Mr. FERGUSON. What do they say? And I have heard some of them talk. But what is the general sense among some of the families and parents that you know about the specific information that they could have with medication guides if they were being gotten into their hands properly?

And we have obviously had a breakdown in the system, and it is normal and natural for parents or anybody who is concerned, who has a conscience, to want to try and figure out who is to blame and where to lay blame about this whole problem. But as we have found, there is a big breakdown in communication and responsibility and jurisdiction.

And that is what we are trying to get to the bottom of. But at the end of the day, what we are finding is that there aren't assurances in the system as we would like them to be today, that every parent who has an SSRI prescribed for their child is getting this information.

Ms. VAN SYCKEL. Right, actually the parents in New Jersey are angry with the doctors because they said the doctors should know when they say it has a black box warning, I heard about increased risk of suicide, and the doctor downplays the side effect. But both parents, one who is a pediatric emergency room nurse at a large hospital in New Jersey, who lost her niece Brittany to a Prozac-induced cardiac arrest and then, of course, with the other teenager, they said had they been provided this information, the horror and the tragedy they endured never would have happened.

And it has weakened the parents who have to make the decisions with their children. It is not the FDA's job. It is not the pharmaceutical companies' job. Parents, we don't want to harm our children. We want the best medical care for them, but I find it insulting that they believe that we don't know how to handle this type of information. Give me the worst scenario, and I will always pray for the best scenario.

Mr. FERGUSON. Mr. Chairman, I know I am out of time, but I think one of the reasons we work so hard on this issue is because at the end of the day, parents are ultimately responsible for the health care of their children. And that is why they go to doctors. That is why they perhaps take medications. That is why you consult with the widest variety and try and gather as much information as you possibly can to make the right decision for your own child. But you are handicapped from making that decision if you don't have all the information. That is why I think this med guide issue is so important.

Ms. VAN SYCKEL. Or if they choose to try the medication at least they have the information to monitor their child.

Mr. FERGUSON. That is right.

Ms. VAN SYCKEL. Because that is really important because we are with our children, 24/7. It is that important, and I have to say this because I believe it is very important. But back during the 2004 oversight and investigation, it was determined by the FDA and by Congress that antidepressants was a causal role in suicide. They used the word causal, but FDA negotiated the label.

And now it is increased risk, and then we have the JAMA study that just came out where they say there is no increase and that the benefits outweigh the risks. But what that JAMA study failed and

what the FDA failed to do was when the child stops taking the medication abruptly, cold turkey, that is when we see our suicide attempts. That is when we see our violent behavior. And FDA, during the adult hearings in this past December, they stopped with their method analysis, their investigation, day 1 of withdrawal. Now if they went for the next 30 days or 4 to 6 weeks, you would have seen some violent behavior, and you would have seen suicide.

And we also have 150 percent increase of prescribing antipsychotics and Strattera to our kids. They also carry suicide labels, and I mean it is pretty sad when I look at the Medechi record in New Jersey and our new doctors, a psychiatrist, is giving it to newborn babies. Risperdal and Effexor, two deadly drugs, how were they administering that to a baby? We need to look into Zyprexa and Risperdal and why they feel the need that they have to medicate our toddlers.

Mr. PALLONE. Thank you so much. Mr. Waxman.

Mr. WAXMAN. Thank you, Mr. Chairman. Dr. Ellenberg, I want to ask you what are the provisions in the administration's PDUFA proposal that allow user fee dollars to be put toward increasing FDA's access to outside population-based epidemiological databases. Information from these databases would obviously be useful for FDA in its efforts to detect safety signals earlier. This is an extremely positive development, and I am encouraged to see that it was included in the negotiated package.

But I think we need to go further in terms of providing FDA with additional tools and authorities. One of IOM's recommendations to Congress was to provide FDA with the authority to require post-market studies. Can you tell us about the benefits and limitations of data mining? Can you also explain why, even if it has the enhanced ability to conduct this so-called data mining, FDA still needs to have the ability to require post-market studies?

Ms. ELLENBERG. Yes. Well, there are a number of different facets to understanding of risks of drugs post-marketing. Data mining is a tool that people have been trying to implement with the passive surveillance system, the reports that people send in. And that can be a useful tool. With several hundred thousand reports coming in every year, you can appreciate there has got to be some kind of automated way to pull out patterns that might need further investigation. And that is what data mining is. So that is one piece of post-marketing surveillance. And that might be the fastest way to actually identify a very, very strange, unusual, very rare adverse event because it could be reported from anywhere.

That is not a good way to identify an increase in a fairly common background rate. So, for example, increased rates of heart attacks with a widely-used drug, you will not find that from a passive reporting system with data mining.

Access to health care databases where you have information on thousands or hundreds of thousands of people and their ability to follow them over time, taking drugs, you might be able to get some information there. So I don't think it is one or the other. And sometimes——

Mr. WAXMAN. You think both are very——

Ms. ELLENBERG. You need both, and you need the ability to sometimes carry out perspective studies that might even need to go beyond existing databases.

Mr. WAXMAN. IOM also concluded that Congress needs to provide FDA with other authorities the agency currently lacks. For example, one, the authority to place a moratorium on DTC advertising and to require the specific warnings be incorporated into DC ads. Two, the ability to require that labels of new drugs carry a special symbol to indicate their newly approved status. Three, the ability to require that companies make label changes instead of just asking them to do so.

Additionally, the IOM has said Congress should enhance FDA's enforcement tools to include things like civil monetary penalties, so that the FDA had other choices besides using its bully-pulpit to threaten using its only real enforcement tool, the nuclear option of removing the drug from the market. Obviously the administration's PDUFA legislation proposal does not incorporate these recommendations.

In your view, if Congress were to act this year only on the drug safety-related provisions included in the administration's PDUFA proposal, would the very serious drug safety oversight problems that the IOM describes in its report be resolved?

Ms. ELLENBERG. Well, as a member of the IOM committee that put the report together, we all felt strongly that the whole package really ought to be adopted, and it was not something to pick and choose, use this one, use that one. So I do believe that these authorities would be helpful.

It is very hard for me or probably anybody to assess really what will happen with this aspect, without this aspect. It would be very hard to predict, but it seems to me that those additional tools could be used by the FDA. Most of the things that you mentioned relate to adequate communication of risk to the public and the issues of what is in the label, ability to regulate DTC advertising. Those are all how do we get information on risks out to the public.

Mr. WAXMAN. Well, along those lines, IOM recommended Congress pass legislation that would require companies to register and report the results from their clinical trials and public available database. Can you tell us what lead to this recommendation and why the IOM felt it was necessary to create a mandatory system?

Ms. ELLENBERG. Well, the concern is that studies may be done that suggest that there may be an increased risk or suggest something that is not favorable about a drug and that if nobody knows that study was done, if that is hidden under regulations, and then other studies are done that maybe don't show that, well it would be hard to know if you have a whole picture, whether this is something we should worry about or not. If we don't see the studies that suggest that there might be a problem, they don't know that there might be a problem.

So there certainly has been a move toward making these public. I think there was a provision——

Mr. WAXMAN. But do you think it ought to be mandatory? Because it could be voluntarily be made public.

Ms. ELLENBERG. I think that many companies are voluntarily making these public. I don't know the extent to which they are doing that now so——

Mr. WAXMAN. Mr. Chairman, if you permit, I have one last question, and I would like to pursue it. We heard from Dr. Galson on the first panel about FDA's system for handling the steadily increasing number of AERs the agency receives, and you describe this trend in your testimony also. He told us they got a half million AERs, and I understand that approximately 200,000 were for serious and unexpected conditions. He said that the staff available to review those reports has been limited by resources. In fact I understand that there are only 20 epidemiologists who review all of those reports.

Dr. Galson also described the upgrades to the agency's IT system that would help to review these reports that FDA would make with an increase of PDUFA dollars for that purpose. But he said it would be only $4 million. I am concerned that that may not be enough. Can you describe in more detail the situation with respect to the agency's review of AERs and comment on whether you think $4 million would be enough to complete what would be a massive overhaul of FDA's IT infrastructure?

Ms. ELLENBERG. No, I don't think $4 million would be enough at all. I think you need probably more than that just to do a reasonable overhaul, a reasonable redo of the adverse event reporting system to incorporate the data mining, making that routine, training reviewers, having enough reviewers to look at it. But as I said before, that is just a single piece, a single component of the needed system. The Centers for Disease Control has a series of databases that they use from the Kaiser Permanente system, and I think they spend something like $10 or $15 million a year to maintain that system so that if there are vaccine adverse events that people are concerned about, vaccine safety issues, they can really go right to that system and try and get answers very, very quickly.

And it is that kind of a linkage of databases that FDA needs to have access to investigate drug safety problems as well.

Mr. WAXMAN. OK, thank you. Thank you, Mr. Chairman.

Mr. PALLONE. Thank you. Dr. Burgess.

Mr. BURGESS. Thank you, Mr. Chairman. Dr. Levine, let me just ask you since this question just came up and you were referenced, do you have a concept of what the dollar expenditure was to develop the data operation that you have at Permanente?

Dr. LEVINE. To develop the data operation?

Mr. BURGESS. Right, the continual data observation that you have.

Dr. LEVINE. I know that the development of our fully automated medical record system, including the inpatient and outpatient pharmacies, is in the billions of dollars. The piece in terms of vaccine safety, which was developed with our Vaccine Center and the CDC, I don't know the cost of the implementation. That was a stand-alone system.

We are currently involved in trying to roll all of our legacy and stand-alone systems into a single fully-automated medical record, which will actually enable projects like the one we did with the FDA and the ones we are doing with the CDC to be done much less

expensively because the maintenance of those legacy systems is extraordinarily expensive. And I share the concern about what you can do with $4 million, just based on what it costs us to do anything in IT.

Mr. BURGESS. Let me ask you a question just to put it in context. How many covered lives are there in Permanente?

Dr. LEVINE. In the present Kaiser Permanente Medical Care Program, there are 8.7 million covered lives. In northern California, it is about 3.35 million.

Mr. BURGESS. But that system which you described that cost *X* million dollars, that covers——

Dr. LEVINE. All 8.7.

Mr. BURGESS. How long did it take to develop that?

Dr. LEVINE. We are midway through the implementation, and development is going hand and hand. We are using software from the Epic Systems, which is one of the largest medical record systems based in Madison, Wisconsin. It was developed for outpatient systems, and we are working with Epic to adapt their product to our very large population.

Mr. BURGESS. And that is probably a topic for another hearing, Mr. Chairman, but it does show the size and the scope of the problem. Dr. Loew, let me ask you, you referenced a figure of 3 percent of medications that were taken off the market. Is that the correct way to phrase that?

Ms. LOEW. That is correct. In the past 20 years, the withdrawal rate has been consistently around 3 percent.

Mr. BURGESS. The withdrawal rate. That is the term you used. Now, of that, can you just give us an idea of what the number of products were that were withdrawn, say, in the last 5 years?

Ms. LOEW. Actually, I don't have that figure, but we can get that data.

Mr. BURGESS. Can you get that for us?

Ms. LOEW. Absolutely.

Mr. BURGESS. And would you have an idea as to how many of those were voluntarily withdrawn by the manufacturer, what problems came to light, and how many of those were enforcement actions by the FDA?

Ms. LOEW. I believe that in many situations, it is a voluntary withdrawal on the part of the manufacturer. A safety issue comes to light. They discuss it with the FDA and decide to withdraw the product from the market, but we will get you the exact data on that.

Mr. BURGESS. OK, I was just thinking back, and I can't recall an instance where there was an actual FDA recall. But I am sure it must have happened, but most of——

Ms. LOEW. The majority of the situations, if I recall, were all situations where the manufacturer had voluntarily taken it from off the market. But I can't verify that.

Mr. BURGESS. Great. If you could get that for us, that would be wonderful. We heard testimony from another witness on the panel that the drug manufacturers, in fact, they don't even pay attention to safety issues after the product has been approved because they have no incentive to do so. Is that an accurate statement?

Ms. LOEW. I would argue that the opposite is completely true. Pharmaceutical manufacturers take the safety of our products extremely seriously. There are, in fact, some extensive requirements for manufacturers to monitor their products in the marketplace, and there are a number of different tools. There are, of course, the adverse effects reporting systems that we have heard about today. If there is a serious adverse event that is detected that is an event that hasn't been previously seen, manufacturers have an obligation to report that to the FDA within 15 days and then to follow up 15 days later with a full report. An additional report quarterly in the first 3 years of production on the marketplace, to quarterly submit reports to FDA on the adverse events that have been detected around the product.

In addition to that, there is an annual report requirement where companies submit all new information that has become available on the product. The manufacturing rate of information, new clinical data, observational data, and so on. They are required to report that, so they take the obligations of monitoring the product in the marketplace extremely seriously. And it is, of course, in their best interest to ensure that is the case and, of course, the best interest of the patients.

Mr. BURGESS. Thank you. Mr. Theriault, let me just ask you, you talked about a number of things that are being done. A company that I became familiar with several years used a labeled isotope in like the parts per billion range to ensure that products were what they said they were, and I think they were talking about rap CDs at the point that they could put this isotope in ink that was on the label and that way, detect whether or not the counterfeit product had found its way into the supply chain.

And I asked the question at that time could this apply to pharmaceutical agents as well because we are talking about a molecule that again would be in the parts per billion range. And the question obviously came up, well, how would the FDA look upon that? Have you had any experience with investigating those types of technologies?

Mr. THERIAULT. We haven't looked at that technology. I think the FDA's preference right now is for RFID tracking, and we have got a pilot project around that right now. But I think one of the issues there is where does the authentication occur? Is it the patient who authenticates the product, the pharmacist, or somebody else in the supply chain? But to answer your question directly, I think that technology probably could apply.

Mr. BURGESS. There was a news story probably 4 or 5 years ago now from New Orleans where they did an analysis of not so much the active ingredient of the medication, but just the inert part of the pill, the vehicle that the medicine was contained in and found significantly high—for medicines purchased over the Internet—and found significantly high quantities of heavy metals, cadmium, liquid chromium. To your knowledge, is that still an ongoing problem?

Mr. THERIAULT. It is. We have seen a number of cases involving heavy metals recently, and I think that the woman who died in British Columbia, I think the coroner said her death could possibly be related to heavy metals that probably she was taking.

Mr. BURGESS. Thank you, Mr. Chairman.

Mr. PALLONE. Let me thank our entire panel for being here this afternoon. I felt this was a good opportunity to hear from you and ask some questions that were really pertinent, and we appreciate it. A number of people asked if they could submit things for the record, both members and panelists. And, of course, we will do that. We will include those things in the record. And you may get additional written questions from some of us in the next 10 days, which we would like you to answer as well in writing. And again thank you all, and I thought it was very good today. We appreciate your help. And with that, the subcommittee meeting is adjourned.

[Whereupon, at 3:05 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

June 7, 2007

Steven K. Galson, M.D., M.P.H.
Director
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Galson:

Thank you for appearing before the Subcommittee on Health on Wednesday, May 9, 2007, at the hearing entitled "Assessing the Safety of our Nation's Drug Supply." We appreciate the time and effort you gave as a witness before the Subcommittee on Health.

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 Member who has submitted the questions and include the text of the Member's question along with your response. In the event you have been asked questions from more than one Member of the Committee, please begin the responses to each Member on a new page.

To facilitate the printing of the hearing record, your responses to these questions should be received no later than the close of business **Thursday, June 21, 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 Edolphus Towns, Member
Subcommittee on Health

The Honorable Mike Ferguson, Member
Subcommittee on Health

The Honorable Marsha Blackburn, Member
Subcommittee on Health

The Honorable Barbara Cubin, Member
Subcommittee on Health

08/23/07 12:47 FAX 006

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

AUG 16 2007

Dear Mr. Chairman:

Thank you for the opportunity to testify at the May 9, 2007, hearing entitled, "Assessing the Safety of our Nation's Drug Supply," before the House Committee on Energy and Commerce, Subcommittee on Health. Steven Galson, M.D., Director, Center for Drug Evaluation and Research, testified on behalf of the Food and Drug Administration (FDA or the Agency). We are responding to the letter of June 7, 2007, you sent in follow-up to that hearing. As instructed in your letter, we have included FDA's responses to the questions asked by each representative on the following separate pages. Your questions are restated in bold, followed by our response.

Thank you again for the opportunity to testify. Please let us know if there are further questions.

Sincerely,

Stephen R. Mason
Acting Assistant Commissioner
for Legislation

Questions from The Honorable John D. Dingell:

1. **The majority of our witnesses at the hearing agree that the Food and Drug Administration (FDA) needs additional resources to effectively do its job. Would the additional resources included in the President's fiscal year 2008 budget and fee increases proposed in the reauthorization of the Prescription Drug User Fee Act (PDUFA) fully fund a robust drug safety program at FDA?**

   Response: Resources are critical to improving our drug safety program. Both the President's fiscal year (FY) 2008 budget proposal and the Prescription Drug User Fee Act (PDUFA IV) proposal include significant additional funding to modernize FDA's processes for ensuring drug safety. With the funds requested, FDA expects to strengthen the science and tools that support the product safety system at all stages of the product life-cycle from pre-market testing and development through post-market surveillance and risk management. FDA also expects to improve communication and information flow among all the stakeholders. The FY 2008 Budget request and PDUFA IV funds would support FDA's ability to effectively detect, communicate about, and act on important safety issues thereby improving patient safety and public confidence in FDA drug safety efforts.

   - **If so, explain why so many stakeholders, some of whom we heard from during the hearing, seem to disagree. If not, how much more is needed and what is the Administration's plan for obtaining the needed resources?**

   Response: We cannot speak for other stakeholders and their assessment of funding needs for FDA. We do believe we will be able to effectively manage our performance on drug safety within our current appropriated funding levels and within the PDUFA IV user fee funding levels.

   - **If additional resources are needed, but are not made available, what drug safety policies would FDA plan to delay?**

   Response: We expect that we can make great strides toward our commitments for strengthening the drug safety system using our existing base resources and the increased budget authority we requested in the President's budget, and the reauthorization of the PDUFA fees.

Questions from The Honorable Edolphus Towns:

1. **Does the Center for Drug Evaluation and Research (Center) [CDER] currently collect and use data from drug clinical trials from cultural and ethnic minorities?**

   Response: Our regulations currently require new drug applications (NDA) to present safety and efficacy date by gender, age, and race (see 21 CFR 314.50(d)(5)(v) and (vi)(a)). Demographics of patients must also be reported in investigational new drug (IND) application annual reports (see 21 CFR 312.33); the annual reports must include the number of patients entered into studies to date, stratified by age, gender, and race. In 2005, CDER published guidance on collection of race and ethnicity data in clinical trials: *http:/www.fda.gov/cder/guidance/5656fnl.htm.*

   Analyses of sub-populations are called for in many other documents including the guidance on how to do a safety review, the template for review of an NDA or efficacy supplement for a product, the 1988 Guideline on the Clinical and Statistical sections of NDAs – which includes guidance on the contents of the integrated summaries of safety and effectiveness, ICH (International Conference on Harmonisation) E-3 provisions, and the ICH Guidance on the Common Technical Document (section 2).

2. **Does any other unit or office within FDA collect such data?**

   Response: Race and other demographics data are collected in clinical trials for products regulated by FDA's Center for Biologics Evaluation and Research (CBER). As noted above, sponsors are required to analyze IND data by race, gender, and age and include the information in their annual reports. (See Title 21, Code of Federal Regulations (CFR) 312.33) NDA regulations require submissions for effectiveness and safety be presented by gender, age and racial sub-groups (21 CFR 314.50.d.5.v. and 21 CFR 314.50.d.5.vi.a.). CBER recommends the same for INDs, NDAs, and biologics license applications (BLAs) and relevant device submissions. Please see page 6 of the Guidance for Industry entitled, "Collection of Race and Ethnicity Data in Clinical Trials" (*http://www.fda.gov/cber/gdlns/racethclin.pdf*). CBER reviews these data.

   Likewise, most studies submitted to FDA's Center for Devices and Radiological Health (CDRH) include age, gender and ethnicity data, which CDRH reviews as part of the submission.

   In addition, FDA's Office of Women's Health is developing a database to collect data on cultural and ethnic minorities as it applies to safe and effective use of drugs in pregnant and lactating women. FDA's Orphan Products Grants program also requires that information about minority and women enrollment be provided on grant applications.

3. **Is such data commonly used when making decisions about drugs particularly related to diseases and conditions experienced by cultural and ethnic minorities?**

   Response: FDA analyzes sub-population effects as part of its routine review of NDAs. However, many studies are not powered sufficiently for any particular sub-group, so that results have to be interpreted cautiously. In most cases, sub-population analyses have indicated the absence of major racial differences. Our approach has been to focus on integrated analysis of safety and effectiveness (see 21 CFR 312.50(d)(5)(v and vi)). These analyses use data from multiple studies and some have been able to detect trends in racial sub-populations.

   For example, in June 2005, FDA approved BiDil, a drug for the treatment of heart failure in self-identified black patients. The approval of BiDil was based in part on the results of the African-American Heart Failure Trial. The study, which involved 1,050 self-identified black patients with severe heart failure who had already been treated with the best available therapy, was conducted because two previous trials in the general population of severe heart failure patients found no benefit, but suggested a benefit of BiDil in black patients. Patients on BiDil experienced a 43 percent reduction in death and a 39 percent decrease in hospitalization for heart failure compared to placebo, and a decrease of their symptoms of heart failure.

4. **How long have you collected these data and what are the trends in terms of participation of cultural and ethnic minorities over time?**

   Response: These data have been submitted in NDAs, INDs, and MedWatch reports for some time. The first official document discussing demographic data was the 1988 Guideline on the Clinical and Statistical sections of NDAs. FDA has not specified patient numbers for demographic sub-groups in clinical trials, however, a guidance issued in September of 2005 made recommendations for categories for ethnicity and race for reporting purposes. The U.S. Government Accountability Office (GAO) did a study of research participants in NDA studies with FDA in 1992 which included data on race, age, and gender of participants. The data from that study showed that participation of black patients was at or above their percentage of the U.S. population.

   a. **Do you believe that the Center for Drug Evaluation and Research should collect such data?**

   Response: As mentioned previously, in September 2005, FDA published a final Guidance for Industry to recommend categories for collecting effectiveness and safety data during clinical trials for ethnic and racial demographic groups. To accomplish this, FDA recommends that the drug manufacturers use the Office of Management and Budget race and ethnicity categories during clinical trial data collection to ensure consistency in evaluating potential differences in drug response among racial and ethnic groups.

In addition in December 2003, FDA sought public comment on whether to amend the MedWatch form to collect race and ethnicity data. After reviewing and considering public comments, we recommended that the MedWatch forms not be changed to add a race/ethnicity data field. There were two primary reasons for this recommendation: 1) race and ethnicity data are not included in the ICH E2B standards (relating to electronic submission of adverse event information), and 2) nearly 95 percent of the adverse event reports received by CDER are from the large Pharma firms and they are now reporting these adverse events electronically using ICH E2B standards. In part, the decision not to include such information in the E2B standards was based on problems with international categorizations of race, and other factors, such as German law, which prohibits collecting and reporting of this type of information.

b. **In your current written plans and reports, do you address the issues related to increasing the numbers of cultural and ethnic minorities in clinical trials?**

See answer below.

c. **If so, please cite these reports. If not, why not?**

Response: FDA currently encourages inclusion of diverse populations in drug development but does not mandate specific numbers of individuals representing demographic sub-groups. In general, FDA staff believes that representation of women, older patients, and African American patients in clinical trials has been in reasonable proportion to their presence in the population without specific mandated requirements.

Requiring substantial numbers of members of each racial or ethnic minority group as well as other sub-groups in the U.S. to be enrolled in each pivotal trial would result in a massive increase in the size of such trials. It would be likely that the benefits of setting sub-group quotas to obtain increased knowledge about sub-group responses to drugs would be outweighed by the burdens in terms of cost of drug development and delays in access to therapy.

In addition, FDA believes there is great potential for the new science of pharmacogenomics to elucidate the mechanistic bases for variations in human responses to drugs. FDA recognizes the importance of pharmacogenomics and encourages its use in drug development.

5. **How does the Center hold pharmaceutical firms accountable for the recruitment of cultural and ethnic minorities, especially concerning new drugs that affect the health and well-being of these communities?**

Response: FDA currently encourages inclusion of diverse populations in drug development but does not mandate specific numbers of individuals representing demographic sub-groups. We do not believe it would be appropriate to require substantial numbers of members of each racial or ethnic minority group as well as other sub-groups in the U.S. to be enrolled in each pivotal trial. It could, for example, result in a drug of value being rejected and made unavailable to everyone because specific numbers of patients in demographic subsets have not been included. The vast majority of drugs appear to behave similarly in all humans and do not show sub-group differences so that in most cases all people would be disadvantaged by this approach. Such a policy could also limit our use of foreign data because foreign populations may have low representation of U.S. minorities. In our guidance documents, we urge companies to study a reasonably representative sample of the intended population.

6. **How does the Center and FDA justify the under-representation of cultural and ethnic minorities in drug clinical trials?**

   Response: The vast majority of drugs appear to behave similarly in all humans and do not show subgroup differences. In our guidance documents, we urge companies to study a reasonably representative sample of the intended population. As noted above, GAO did a study of research participants in NDA studies with FDA in 1992, which included data on race, age, and gender of participants. The data from that study showed that participation of black patients was at or above their percentage of the U.S. population.

7. **The National Medical Association (NMA) has urged FDA to assess monetary penalties against researchers who conduct clinical drug trials that lack significant participation from minorities. What is your view of the NMA's position?**

   Response: The Administration does not have a position on this issue at this time.

8. **Minority exclusivity provisions have increased minority participation in pediatric studies. Do you believe that these provisions would work in other areas of study as well?**

   Response: The Administration does not have a position on this issue at this time.

Questions from The Honorable Mike Ferguson:

1. **As is evident in the Senate PDUFA legislation, there is widespread interest in ensuring that the appropriate incentives for antibiotic product development are in place. An important part of that equation is setting the proper standards for approval. While I fully support my colleagues who have been examining the use of non-inferiority studies to support certain antibiotic product approvals, I think we all would agree that FDA needs to respond carefully to the aforementioned concerns.**

   Response: Yes, in more serious infectious diseases where antibacterial drugs are reliably known to have a large treatment effect, and prevent the serious consequences of untreated infection, non-inferiority studies remain an appropriate type of study for evaluating the safety and efficacy of antibacterial drugs. However, there may still arise certain circumstances in serious diseases where no drugs are known to be effective and for which a non-inferiority trial design would be non-informative, and therefore, inappropriate. In these situations, a superiority trial, e.g., either against placebo or a non-approved comparator product, may be a more appropriate study design.

   Can you address my concern that FDA not place an unreasonable burden on companies seeking approval of products to treat serious infections?

   Response: FDA is committed to providing advice to sponsors to establish acceptable approaches for determining non-inferiority margins in diseases where non-inferiority designs are appropriate.

2. **Although there are challenges associated with some non-inferiority trials, it is generally accepted that there are cases where non-inferiority trials are the only ethical and/or feasible means of establishing a drug's efficacy and safety. For example, it would be unethical for patients with serious, life-threatening conditions to be enrolled in a placebo trial, where they could die or lose limbs to infection in order for a drug's efficacy to be established. The other alternative would be a superiority trial, which may in certain cases be so large and difficult to conduct that the time and investment required to achieve approval would be prohibitive or impossible. The current lack of new antibacterial development for serious conditions should not be exacerbated by prohibitive trial requirements.**

   Response: FDA is aware of the ethical concerns related to studying certain types of infectious disease in placebo-controlled trials. FDA would not require a study design that we believe would compromise patient safety. FDA is committed to working through these important and often challenging issues with sponsors.

Page 8 - The Honorable John D. Dingell

Questions from The Honorable Marsha Blackburn:

1. **What kinds of "best practices" are being used at FDA to isolate internal problems for resolution?**

   Response: We are focusing on developing both our people and processes so that CDER has a culture that respects differing points of view and is more inclusive in discussions and decisions. We have utilized Process Improvement Teams with broad representation to identify and address process issues between the Office of New Drugs (pre-market team) and the Office of Surveillance and Epidemiology (OSE) (post-market team). We have enlisted the help of experts in organizational development to work with staff and management to determine specific internal problems and to assist in the development of good communication skills across and between both groups. We received recommendations about specific internal problems from the Institute of Medicine (IOM) Drug Safety Report and are taking specific actions to address those recommendations (FDA response to IOM Report, January 2007).

2. **I am concerned about the institutional will and corporate culture at FDA. Does FDA have the will to make institutional changes and shift its culture to address its problems? How is FDA changing its corporate culture to address internal problems?**

   Response: Significant culture change is an evolving process that will not happen quickly; however, FDA is committed to managing this process. Our general aims in changing the climate at FDA includes: 1) vigorously promoting scientific debate inside the Agency, 2) promoting respect of differing points of view, 3) establishing more transparency in communications across all units of the Agency, and 4) establishing processes for decision-making that are more inclusive.

3. **Congress can provide FDA with all the money in the world, but funding does not necessarily solve problems. Are FDA's problems a question of funding or will? Does FDA have the drive to correct institutional problems that do not have a price tag? How is this being accomplished?**

   Response: You are correct that not all institutional problems have a price tag; however, we expect that resources proposed in the President's budget and the PDUFA funding will support a larger staff, particularly for monitoring safety issues, easing some of the staff workload issues. We have already made some changes to address institutional problems including: 1) establishing a management philosophy of integration across organizational lines, 2) elevating OSE to report directly to the Center Director, 3) developing a comprehensive strategy for improving our culture, with the assistance of experts in organizational culture, 4) establishing an Associate Director for Safety and a Safety Regulatory Project Manager in each Office of New Drugs (OND) division, and 5) conducting regular meetings between the OND divisions and OSE staff.

Questions from The Honorable Barbara Cubin:

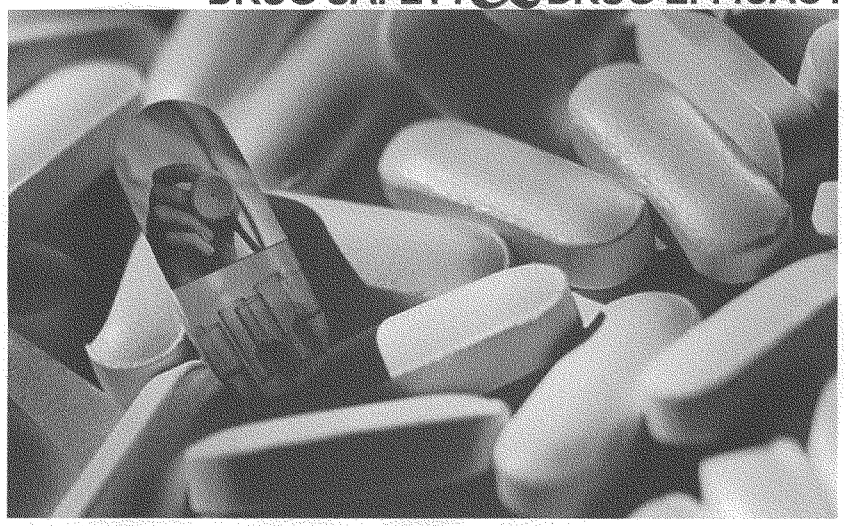
1. **As I understand it, an additional $4.6 million in user fees in FDA's recently proposed reauthorization of the Prescription Drug and User Fee Act would help support the development of clinical trial guidance documents.**

   For the second Congress in a row, Representative Brian Baird and I have introduced legislation that, in part, requires FDA to publish clinical trial guidelines for antibiotics. Section 10 of H.R. 1496 requires FDA, within one year of the date of enactment of the legislation, to publish clinical trial guidelines for "antibiotic drugs, including antimicrobials to treat resistant pathogens, bacterial meningitis, acute bacterial sinusitis, acute bacterial otitis media, and acute exacerbation of chronic bronchitis." Additionally, Section 10 requires that the guidelines indicate "the appropriate animal models of infection, in vitro techniques, and valid microbiologic surrogate markers." Finally, Section 10 requires that within five years of the enactment of the legislation, the guidelines be reviewed and updated by FDA "to reflect developments in scientific and medical information and technology."

   I have identified a need for these guidelines to spur more timely and effective anti-infective drug development. It is my understanding that similar guidelines have been under development at FDA since at least 2002, and I respectfully request a written response detailing the progress of these guidelines and when FDA plans to publish them.

   Response: It has proven challenging to provide clear, unambiguous guidance for industry on new approaches to the approval of these drugs, as our understanding of the use of non-inferiority studies to support regulatory approval of antibacterial products has been evolving over recent years. When we are proposing a new paradigm for clinical trials, it is particularly challenging. We have been developing draft guidance documents that will discuss these issues for specific antibiotic drugs. Two of these draft documents are nearly complete but will need to receive higher organizational clearance before publication.

DRUG SAFETY & DRUG EFFICACY



TWO SIDES OF THE SAME COIN

A Proposal for Improving Drug Safety, Ensuring New Drug Access, and Strengthening the FDA

a white paper
REPORT
2007

The following document represents the collective view of expert academic scientists and clinicians, research advocates, and representatives of the patient community. This committee was convened in order to recommend ways in which policy makers in the United States Congress and the United States Food and Drug Administration (FDA) could further strengthen product evaluation. Individuals on this panel have expert knowledge of FDA processes, drug safety, product development, and scientific and clinical research. They have volunteered their time and expertise for the benefit of the patients and the public.

TWO SIDES OF THE SAME COIN

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EXECUTIVE SUMMARY

Efforts to increase the effectiveness and efficiency of FDA are important and well justified. The agency is currently facing the challenge of strengthening the product safety review process at both pre-approval and post-marketing stages. In the view of this committee, drug efficacy and safety should continue to be evaluated simultaneously by the existing FDA division that is most familiar with the product under review.

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FDA currently lacks the resources and personnel to fully integrate the science and technology necessary to develop a systematic approach to safety surveillance. This type of approach would utilize a variety of sources to routinely identify and obtain accurate data, employ computational and statistical tools to analyze large-scale information sets, and incorporate emerging scientific tools to distinguish and describe safety and efficacy signals.

In addition to resources, FDA will require employee training programs and a commitment to the advancement of science through the Critical Path Initiative to strengthen safety monitoring. While it does provide useful information, the current passive surveillance method is not as efficient as it could be in detecting emerging safety and efficacy data. An automated and routine approach to drug monitoring will improve the agency's ability to earlier identify risks of marketed new drug products and to evaluate these in the context of the health benefits provided by the product.

A benefit-risk approach across a product life cycle is the cornerstone of drug development and should be the foundation of drug regulation as well. This is particularly true with regard to drugs for serious and life-threatening diseases. In such circumstances, it is reasonable to accept a greater level of risk to produce even a modest benefit. This view provides the foundation of accelerated approval as well as fast track and priority agency review. Consideration must be given to the condition the drug is meant to treat as well as to the extent of the patient's disease, its duration and its impact on the patient's functional status and quality of life. Depending upon the particular illness, drugs can potentially be designed for and used at a specific point in the continuum of disease from prevention to terminal illness.

To focus solely on drug safety without consideration of drug benefit, including the severity of the underlying disease or condition, effectiveness of the product under evaluation, and availability and utility of alternative therapies, will create a chilling effect on the development of new treatments for patients most in need of innovation.

Burdensome new requirements may reverse the trend of hard won innovations created during the last fifteen years, without reducing the risks that can only be uncovered through long-term study or experience in large populations. Innovations were made consciously in the 1990s to protect Americans by ensuring that: (1) effective new therapies move to market as rapidly as possible; (2) drug development and manufacturing remain in the U.S.; (3) treatments for unmet medical needs of serious and life threatening diseases are expedited and; (4) patients have the opportunity to accept greater risks (within recognized standards) for greater potential benefit. While ensuring safety of new drugs is extremely important, only a small portion of the ultimate safety profile is evident at the time of initial drug approval. It is equally important to preserve those elements that have contributed to great improvements to the lives of patients and encouraged continued scientific innovation.

The 110th Congress will reauthorize the Prescription Drug User Fee Act in 2007. There is little doubt that drug safety will become a central feature in the debate surrounding the Act's renewal. In addition, Congress will consider other legislation regarding potential

FDA reform. This is an opportunity to strengthen and increase the capabilities and efficiency of FDA in all phases of its work. Several proposals will receive careful consideration, including the Enhancing Drug Safety and Innovation Act of 2007 (S.484) and the Institute of Medicine's recent report on drug safety. While recent policy recommendations contain elements that would provide assistance to an overburdened agency, proposals focused on increasing FDA authority and regulatory oversight do not fully address ways to preserve recent innovations and improvements in public health.

To strengthen the effectiveness of the current system, the agency needs to develop and implement a routine and automated approach to safety surveillance. Therefore, new policy should focus upon shifting the emphasis of drug safety away from simply risk management, and instead, focus upon establishing an efficient and systematic method of benefit-risk assessment.

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The goal of this report is to provide lawmakers with a balanced perspective from a broad group of physician investigators and advocates who have extensive experience in the field of drug development for patients with serious diseases. Our desire is not to contest what is contained in other reports. It is of the utmost importance to ensure that new legislation achieves the goal of enhancing the drug approval and monitoring process, as well as optimizing the productivity of FDA. Unintentional consequences such as restricting or slowing patient access to life-saving treatments or discouraging innovative product development would be extremely detrimental. Over-regulation and subsequent slowing of the drug approval process increases the cost of medical care, thereby decreasing access to medications because of their expense.

To best position FDA for continued success, the committee encourages members of Congress and FDA officials to implement policies to address the following recommendations.

RECOMMENDATIONS

1 Continually and simultaneously evaluate safety and efficacy when determining public access to, and marketing of, new products

- **1.1.** Ensure that the regulatory process reflects the essential balance of benefit and risk that is fundamental to all medical decision-making
- **1.2.** Discourage new policies that duplicate existing mechanisms or unnecessarily slow FDA evaluations of new agents
- **1.3.** Ensure that up-to-date information is accessible to patients and health care providers at the time a prescription is written

2 Improve information technology and increase training to strengthen the effectiveness of FDA

- **2.1.** Improve informatics systems within FDA
- **2.2.** Increase training of FDA personnel to enhance agency effectiveness and standards
- **2.3.** Capitalize on the unique expertise at FDA
- **2.4.** Minimize future leadership gaps at FDA

3 Enhance existing infrastructure for adverse event reporting and analysis in order to improve post-market safety monitoring

- **3.1.** Improve the existing tools for adverse event reporting to enable systematic post-market surveillance
- **3.2.** Engage public-private partnerships to aid in safety monitoring and data management
- **3.3.** Examine electronic medical records as a potential data source to enhance the Adverse Event Reporting System
- **3.4.** Equitably share funding for programs to ensure the safety and efficacy of new products between public and private sources

4 Advance current scientific opportunities to create a stronger, safer, science-based FDA

- **4.1.** Increase support for the Critical Path Initiative to modernize FDA
- **4.2.** Prioritize discovery, evaluation, validation and clinical application of new biomarkers to improve drug evaluation and refine drug prescribing

INTRODUCTION

INTRODUCTION: An Overview of the Current Climate

The United States Food and Drug Administration (FDA) serves as the nation's agency for protecting the public from dangerous and ineffective drugs, devices, and foods. Despite its longstanding reputation as the world's "gold-standard," lawmakers and the general public have recently questioned the agency's policies and decisions related to drug safety. Perhaps the most recognized example is Merck's recent removal of rofecoxib (Vioxx®) from the market. FDA has been accused of failing to act in a timely manner as well as not having the proper authority to react to emerging information about potentially harmful products. In the case of rofecoxib, the manufacturer voluntarily removed the product from the market after a clinical trial for an additional indication revealed an increase in cardiovascular events among patients receiving the drug.[1,2]

The agency is currently experiencing a decline in public confidence due in part to the debates surrounding rofecoxib and a handful of other similar product removals.[3] This perceived lack of public trust in the agency that regulates nearly one-quarter of the U.S. gross domestic product[4] has seriously affected morale of current FDA employees and discouraged qualified candidates from seeking jobs at FDA. It has also led to a wide range of proposals for improving drug safety, including establishment of new offices within FDA devoted exclusively to post-market safety evaluation.[5] Others have called for a private agency to be responsible for addressing safety concerns.[6] We maintain that safety cannot be evaluated without concurrently considering efficacy.

> Safety cannot be evaluated without concurrently considering efficacy.

The simultaneous analysis of both a product's benefits and risks formally evaluated by the pharmacological measurement of "therapeutic index" is critical to the assessment of any drug product and should be central to the FDA approval process. This element is so important that calls to isolate safety and efficacy evaluation from one another prompted Center for Drug Evaluation and Research (CDER) Director Dr. Steve Galson to say, "I think this is really, really a dangerous recommendation [to break up CDER] and will, if it is ever implemented, be to the severe detriment of patients and to the development of new products."[7,8]

> As billions of prescriptions are filled annually, it is important to recognize that every drug has benefits and risks associated with its use.

As billions of prescriptions are filled annually, it is important to recognize that every drug has benefits and risks associated with its use. If new drugs were to be allowed to enter the marketplace based solely on efficacy data, they might possess unacceptable, unknown or poorly understood risks. Conversely, if an effective new treatment is withheld from the marketplace because there is a chance that it could pose a risk to a particular user, new therapies would never become available to patients. Consequently, FDA must simultaneously evaluate benefits and potential hazards associated with any new drug. By doing so, the agency can ensure that drugs with the greatest benefits and fewest side effects for the intended users reach the market.

A "one-size-fits-all" approach to benefit-risk assessment and drug approval cannot be used because each disease and treatment setting is different. Likewise, the treatment challenges based on the continuum of illness, from prevention of mild illness to therapy for life-threatening disease, also vary. For example, acceptable risks or side effects for treatment of patients with late-stage AIDS are far greater than those for treatment of mild arthritis.

> ...Acceptable risks or side effects for treatment of patients with late-stage AIDS are far greater than those for treatment of mild arthritis.

Therefore, mandating a one-size or standard requirement for approval based solely upon efficacy or safety is inappropriate, and treatment options should be evaluated based on an informed decision regarding the benefit-risk profile offered by a particular agent for a specific disease setting. This was the same rationale that fueled major innovations to the agency in the 1990s. Programs of accelerated drug approval, priority review and fast track

were designed to fulfill minimum safety requirements in smaller patient populations and were justified by the potential of the therapy tested to meet serious unmet medical needs.

Post-approval monitoring by FDA is essential to further characterize a drug's impact on public health after it has been introduced into the marketplace. The reality is that rare and serious side effects may emerge only after thousands or hundreds of thousands of patients are treated with a product.

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This may be related to pharmacogenetic factors resulting in differing metabolism of drugs by certain patients. This can occur with any product and often may not be identifiable in the pre-approval stages. Therefore, comprehensive and accurate information about risk must be continuously made public while there is continued access to a drug. This process allows individual patients and their health care providers to make the most informed decisions as to what treatment regimen presents the greatest degree of benefit with an acceptable level of risk.

Product approval decisions made at FDA affect every American citizen. **In 2005, pharmacists filled nearly 3.2 billion drug prescriptions (*Figure 1*).** All of these drugs initially required FDA approval in order to reach the individuals who rely on their benefits. That figure does not include non-prescription products that are also regulated by FDA.

Because of its extensive impact on the population, the FDA approval process is at the forefront of the discussion among government officials and stakeholders as they consider changes to drug evaluation and safety policy and practice. Legislation under consideration includes the reauthorization of the Prescription Drug User Fee Act (PDUFA) in 2007. User fees are funds paid to the agency by product sponsors to offset the costs associated with FDA review. It is likely that the reauthorization of the Act will be accompanied by debate on the expansion of user fees to apply to safety evaluation and monitoring at FDA. Additionally, multiple bills in Congress, if passed, would change current FDA procedures and function.[5,9,10] It is of the utmost importance to ensure that any new legislation achieves the intended improvements or refinements to FDA, while improving the timeline for drug approval.

While recent policy recommendations contain elements that would temporarily provide assistance to an over-burdened agency, proposals focused on increasing FDA authority and regulatory oversight are not the most effective or direct way to enhance safety surveillance and continue to improve public health. In fact, an increase to the agency's authority could result in unintentional consequences, such as restricting or slowing access to life-saving treatments by patients in need, or discouraging innovative product development. Furthermore, over-regulation and subsequent slowing of the drug approval process increases the cost of medical care and could adversely affect access to medications because of their expense. This would be extremely detrimental for patients and the public. To strengthen the effectiveness of the current system, the agency needs to develop and implement a more systematic and automated approach to safety surveillance.

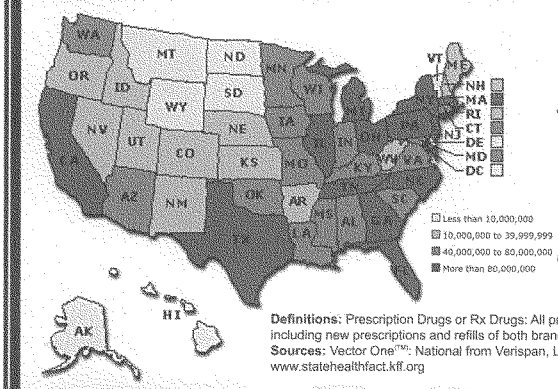
By utilizing drug safety and efficacy information from a variety of sources, such as established healthcare networks like Kaiser or UnitedHealth Group, FDA could actively evaluate and respond to signals more efficiently. New policy should shift the emphasis of drug safety away from simply risk management, and instead focus upon systematic methods of benefit-risk assessment based on improving the information upon which decisions are made.

DEFINED
Systematic Safety Surveillance:
A robust safety system that would utilize existing medical databases and electronic health records to routinely identify accurate data, employ computational and statistical tools to analyze large-scale information sets, and incorporate emerging scientific tools to distinguish and describe safety and efficacy signals.

The agency has already taken a number of important steps to improve the current system. For example, FDA is currently working to identify additional sources of safety data such as claims data available from the Centers for Medicare & Medicaid Services (CMS).[11] While FDA has generally been successful in meeting product review timeline goals, it continues to strive toward increasing efficiency and productivity by further streamlining the product review process. However, for FDA to continue to best serve the public health, the agency must improve upon current drug safety systems by implementing a collaborative and systematic approach to surveillance and applying new emerging technology. As science evolves, the expertise and evaluation methods at FDA must keep pace. To do so, and to maintain the gold-standard of product evaluation, increased resources are essential.

This document represents the collective view of the assembled panel. It is the belief of this committee that considering the number of products used and the number of individuals treated, FDA has done an exceptional job of serving and protecting the

FIGURE 1 Total Number of Retail Prescription Drugs Filled at Pharmacies in 2005



In 2005, pharmacists filled nearly 3.2 billion drug prescriptions

Definitions: Prescription Drugs or Rx Drugs: All products filled by retail pharmacies, including new prescriptions and refills of both brand name and generic drugs.
Sources: Vector One™: National from Verispan, L.L.C.: Special Data Request, 2006, www.statehealthfact.kff.org

Retail Prescriptions Filled by State

California	263,362,832	Connecticut	41,735,882
Florida	236,805,668	Oklahoma	41,297,607
Texas	227,796,113	Iowa	41,099,023
New York	199,322,763	Colorado	38,117,032
Pennsylvania	139,048,024	Arkansas	35,945,090
Illinois	129,886,624	Kansas	33,798,011
Ohio	126,067,848	Oregon	33,473,641
North Carolina	110,796,989	West Virginia	27,860,454
Georgia	102,573,382	Utah	22,475,354
Michigan	98,162,069	Nebraska	19,779,916
Tennessee	91,475,983	Nevada	19,136,956
New Jersey	88,931,100	New Mexico	16,418,349
Massachusetts	80,557,252	Maine	14,598,381
Indiana	77,394,034	New Hampshire	13,584,643
Virginia	76,821,175	Idaho	12,614,196
Missouri	75,598,569	Rhode Island	12,300,806
Wisconsin	65,436,881	Delaware	9,542,986
Alabama	65,415,926	Montana	9,073,366
Kentucky	63,657,530	Hawaii	8,982,212
Louisiana	63,321,727	South Dakota	8,354,738
South Carolina	61,684,275	Vermont	6,893,912
Arizona	56,783,635	North Dakota	6,109,530
Maryland	55,786,372	District of Colur	5,268,896
Washington	53,655,217	Wyoming	5,063,076
Minnesota	52,294,557	Alaska	4,214,437
Mississippi	42,265,987		

public. In fact, since the first authorization of PDUFA, only 3.5% of approved drugs have been subject to safety-based withdrawal (12/345). This is similar to the ratio of pre-PDUFA safety-based withdrawals (3.1%, 15/488).[12] However, for sustained improvements in drug safety to occur, **the emphasis should be shifted from regulatory authority and risk management strategies to creating a systematic approach to post-market surveillance**. The agency requires a system that utilizes various sources to identify and obtain accurate data, has the computational and statistical ability to routinely analyze large-scale information sets, and incorporates emerging scientific tools to improve the methods of identifying and anticipating safety and efficacy signals. To create this systematic approach to drug surveillance **FDA will require significant additional new resources, employee training programs, and a commitment to the integration of science through the Critical Path Initiative**. An automated and systematic approach to drug monitoring will improve the agency's ability to earlier identify benefits and risks of marketed new drug products. This will allow the agency to improve communication of both the benefits and risks of products internally as well as to manufacturers, health care providers, physicians and patients. **Drug efficacy and safety should not be evaluated separately**, and increased product information will allow well-informed decisions to be made between physicians and patients about the use of potentially life-saving or life-extending therapies.

In order to comprehensively address the needs of FDA, the committee presents the following recommendations.

RECOMMENDATIONS

RECOMMENDATIONS

1. Continuously evaluate both safety and efficacy when determining public access to new products

1.1 Ensure that the regulatory process reflects the balance of benefit and risk

Patients and health care providers routinely consider the issue of drug safety when addressing potential treatment options. In practical terms drug safety is never considered in isolation from potential efficacy, especially for patients who are facing a serious or life-threatening illness. The potential benefits of a drug and the risks associated with it must be considered together and the decision to allow its use will be influenced by the specific disease setting in which it will be used. The level of acceptable risk will vary with the seriousness of the illness, the goals of therapy and the spectrum of available treatment options.

> The level of acceptable risk will vary with the seriousness of the illness, the goals of therapy and the spectrum of available treatment options.

For instance, a young parent with late-stage pancreatic cancer would likely be more willing to accept a therapy with a relatively high risk of adverse side effects for the chance to extend his life. In contrast, an individual with a relatively low risk for developing cancer would accept very little risk from a preventive medication. At the level of medical practice, safety and efficacy are always considered together by the treatment professional in the context of a patient's specific circumstances and preferences. The regulatory process should reflect this essential balance that is fundamental to all medical decision-making.

1.2 Discourage policies that duplicate mechanisms of FDA benefit-risk evaluations

At the regulatory level, FDA must simultaneously and carefully consider both safety and efficacy when determining public access to new drugs. While proper safety evaluation is necessary, creating undue burdens or additional hurdles in the regulatory process would inevitably create delays in the approval of new drug products. New policies that duplicate existing mechanisms or complicate agency procedures should be avoided so as to not lengthen the overall review process and limit patient access to new therapies.

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The review division within FDA's Office of New Drugs (OND) develops the necessary expertise on the medication, including its safety profile, during the process of evaluating the Investigational New Drug application (NDA) and all phases of clinical research leading up to the NDA submission for marketing approval. OND reviewers consult with staff from FDA's Office of Surveillance and Epidemiology, who provide expertise in post-marketing safety issues, including epidemiology, evaluation of adverse event data, and risk management techniques. Pre- and post-marketing safety data are integral and interrelated, and review and safety staff work closely in determining what regulatory actions are appropriate for a particular new drug, taking into consideration risk and benefit information from pre- and post-approval sources. It would be inefficient and virtually impossible to try to re-create the OND staff's level of expertise if responsibility for post-market safety were to be housed in a separate safety center within FDA. In addition, it would be unwise, expensive and obstructive, to transfer safety authority to personnel who focus solely on safety and may not have a deep understanding of the clinical need for a drug and its potential therapeutic benefit. This could result in safety officers being asked to make decisions without the full range of knowledge acquired by the experts who have reviewed the product through all phases of development.

Most importantly, experts in drug safety may not have the knowledge and clinical expertise that is essential to adequately evaluate a drug for an intended use, where knowledge of the clinical manifestations, natural history

and range of available therapies for a particular disease is required to determine if a particular safety profile is medically acceptable. Furthermore, excessive regulatory barriers could ultimately discourage manufacturers from pursuing new products because of potential safety concerns that may be inherent but manageable in particular drugs that treat life-threatening illness.

The case of cisplatin illustrates this point: this drug is essential for the treatment of testicular cancer, despite potentially harmful side effects.[13] The development of cisplatin completely revolutionized the therapy of this disease, converting it from a highly fatal illness to one that is curable in the majority of patients. Notably, cisplatin also can cause kidney failure, dangerous electrolyte disturbances, deafness and nerve damage. Indeed, this lifesaving drug also increases the occurrence of cardiovascular events by over 2.5-fold.[14] Nevertheless, experienced oncologists can manage nearly all of these side effects effectively, and cisplatin remains a mainstay in the treatment of testicular cancer, ovarian cancer, lung cancer and other tumors. We are concerned that a product analysis based on safety alone would potentially reject such a drug due to its significant toxicities to multiple organ systems, even though the drug offers the potential for cure to some patients and significant prolongation of life to many others.

Fortunately, the FDA processes currently in place evaluate the benefits and risks of an agent when determining whether a drug should receive marketing approval. An independent evaluation of safety would run the risk of creating different standards for new therapies.

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If cisplatin had been withheld from market based upon the safety profile, hundreds of thousands of patients would have never experienced the benefits of this treatment. In the case of this and other cancer therapies, patients have accepted a relatively severe side effect profile in return for improved longevity and quality of life. A similar example is Tysabri® which is used for treatment of multiple sclerosis. The manufacturer voluntarily removed it from the market due to severe yet exceedingly rare neurotoxic side effects, despite the genuine improvement it brought to the lives of many patients and their families, which no other medication could provide.[15] It was only after an FDA advisory committee recommendation that considered the degree of risk as well as potential for benefit that it has again become available with additional labeling.[16] In this instance, not only are many patients willing to accept potential risks, but physicians or other prescribers can use the extent of the disease to tailor treatment regimens to minimize that risk and achieve benefit.[17,18,19]

A CLOSER LOOK:

DRUG: cisplatin

WHAT IT DOES: It is essential for the treatment of testicular cancer

RISKS: kidney failure, dangerous electrolyte disturbances, deafness and nerve damage; increase in occurrence of cardiovascular events

BENEFITS: Converts cancer from a highly fatal illness to one that is curable in the majority of patients
Experienced oncologists can manage nearly all of these
side effects effectively, and cisplatin remains a mainstay in the treatment of testicular cancer, ovarian cancer, lung cancer and other tumors

WHY IS THIS IMPORTANT? A product analysis based on safety alone would potentially reject such a drug due to its significant toxicities to multiple organ systems, even though the drug offers the potential for cure to some patients and significant prolongation of life to many others

Many of these benefit-risk decisions are difficult and will evoke disagreements even among experts. Such scientific debate commonly occurs in the case of complex scientific questions within the world's most respected medical institutions. The public should not view debate and scientific discourse as reflecting negatively upon FDA. Rather the public should be reassured that the agency is receiving broad-based input and examining all aspects of every drug application before making final decisions on drug marketing, labeling and access.

1.3 Ensure that up-to-date information is accessible

To ensure that appropriate benefit-risk assessments are made by patients and physicians, it is imperative that up-to-date information be accessible at the time of the prescribing decision. This must include accurate data regarding patient condition as well as current treatment options. Efficient dissemination of such information is critical. Steps to enhance communication could include improved accessibility and clarity of product inserts, increased non-promotional information on the FDA website, and enhanced alerts sent directly to physicians or other prescribers of medication. Communicating this information to patients, physicians, and other health care providers should be the responsibility of both the product sponsor and FDA. In order for FDA

to successfully enhance communication plans, additional resources will be required.

2. Improve information technology and increase training to strengthen the effectiveness of FDA

2.1 Enhance informatics systems within FDA

Many have called for new methods to increase the breadth and accessibility of drug safety data available to FDA. However, the success of such approaches will depend heavily on improving the IT infrastructure of the agency. Total spending on IT-related activities in 2004 at FDA was $29.1 million less than the agency's request for these activities, a funding decision influenced by pressures on Congress to restrain discretionary spending. The difference between the budget request and the Congressional appropriation exceeds the entire $23.8 million budget of the FDA's Office of Drug Safety for 2004.[20] FDA officials say, "...we need to improve our analytical tools and approaches for evaluating information and turning raw data about drug-safety related questions into practical medical facts..."[21] With the proper technology resources to improve infrastructure, FDA could routinely and systematically evaluate data from completed and ongoing clinical trials and registry studies, perform useful epidemiological studies, and characterize population subtypes and their response to treatments.

> With the proper technology resources to improve infrastructure, FDA could routinely and systematically evaluate data.

In addition, greater ability to compare and combine data across different sources would result in greater flexibility and improved efficiency and the potential to generate novel insights about vulnerable populations. This includes the ability to share information regularly with the Center for Medicare and Medicaid Services and with sister agencies within the Public Health Service, including the National Institutes of Health and the Centers for Disease Control and Prevention. Just as FDA needs enhanced infrastructure and information systems, it also needs adequate personnel training to meet emerging technology advances. Increasing the number of IT trained staff is essential for the overall advancement of the bioinformatics systems. As the agency strives to monitor and evaluate the treatments of the future, it is imperative that FDA has the resources to effectively manage and interpret the wealth of information currently available.

2.2 Increase training of FDA personnel

FDA needs to attract and retain a greater number of talented employees in order to perform accurate benefit-risk assessment, evaluate new therapies and implement the Critical Path Initiative. As the FDA workload grows, so too must the resources to recruit and increase staff with critical competencies. This has become increasingly difficult due to a relatively non-competitive pay scale at government agencies. In addition, increased training of FDA personnel will also enhance agency effectiveness and standards. FDA should create opportunities for employees to spend time in clinical care settings and participate in productive academic or commercial research sabbaticals in order to provide employees with valuable first-hand experience in drug development and clinical trial design. Collaborations with academic and industry partners would be viewed favorably by all parties and would be mutually beneficial in achieving common goals. These partnerships exist now with FDA detailees serving within HHS, its agencies and within the Congress. Collaborations should also be developed with academic medical institutions and private industry to expand the experience of FDA medical and scientific staff in drug discovery, development and application in clinical practice. Such partnerships would ensure that new and advancing technologies are being evaluated by highly trained personnel. Furthermore, employee professional growth will lead to greater internal advancement and employee retention, and will create an encouraging environment for career opportunity. However, without significant additions to FDA personnel, such a program cannot be implemented.

2.3 Capitalize on expertise at FDA

To ensure that FDA retains its highly qualified personnel, the agency should encourage its scientists to take greater intellectual leadership roles in areas of their particular expertise. For example, with appropriate resources, experts at FDA could be leaders in developing risk assessment models and computer applications for the evaluation of medical data.

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The in-house expertise at the agency could provide unique contributions to the next generation of computer models that monitor evolving statistical endpoints, aid in the normalization of background signals, and identify potential early warning signs of side effects or unanticipated toxicities. Additionally, FDA experts could play an integral role in the

development of advanced clinical trial designs that achieve greater efficiency and permit definitive conclusions to be obtained more quickly. Such advancements to the current clinical trial system could result in improved pre-market product evaluation, smaller trial sizes, more efficient dosing determinations, and ultimately, safer products reaching patients faster.

2.4 Minimize Future Leadership Gaps at the FDA

A fully functional and efficient agency requires a strong leader. Confirmed, stable leadership at FDA strengthens the agency and benefits not only the scientific community but the public it serves. In recent history, FDA has had a confirmed commissioner for only 18 months of the past almost 6 years.[22] This compromises the agency because strong leaders are needed to make difficult decisions on issues ranging from resources, staffing, regulatory tool development, product actions and safety, to internal and international harmonization. Top FDA officials have openly commented, "It's been particularly tough because we haven't had a confirmed commissioner who has been able to be the spokesperson and be the advocate for the FDA…I think that has hurt our ability to respond to criticism."[23] Congress should attempt to maximize the expertise and tenure of the FDA leader and should avoid confirmation delays based on politically sensitive issues. Additionally, the implementation of a formal succession plan would help to reduce future leadership gaps. In this way, the public will have increased confidence in the agency and in the products it regulates.

3. Enhance existing infrastructure for adverse event reporting and analysis in order to improve post-market safety monitoring

3.1 Improve the existing system for adverse event reporting

To enable better post-market surveillance, the existing system for adverse event reporting must be expanded and improved and new systems for surveillance should be developed. In 1993, FDA began using the MedWatch program, which allows consumers, physicians, and other trained providers to report adverse events that they suspect are associated with drugs or medical devices.[24] Reports go directly to FDA and become a part of the Adverse Event Reporting System (AERS). AERS, a computerized database of these reports, is the agency's primary post-market safety surveillance system.[25] FDA receives over 400,000 reports of adverse events annually.[26] The majority of reports come from manufacturers, who are required to file reports of serious, unanticipated events associated with their products.[27] However, it has been estimated that the current voluntary MedWatch system only receives 1-10 percent of all of the adverse events that actually occur.[28] While the accuracy of this number is debatable, due to the likelihood that certain types of serious events are reported more frequently than non-serious events, there can be little doubt that the voluntary reporting system only receives a fraction of adverse event data. Despite these limitations, physicians and other medical prescribers do need easy access to adverse event report analyses and should utilize the information to optimize treatment for their patients. Additionally, because healthcare providers are uniquely positioned to determine potential causal associations between an adverse event and a drug, they should be better informed about MedWatch with respect to how and when to report adverse side effects.[29,30] While the MedWatch system does not establish definitive causality for any particular adverse event, it does provide signals of potential toxicities.[31]

The voluntary reporting system should be retained and strengthened and supplemented with routine healthcare professional education. This will facilitate and encourage healthcare professionals to improve reporting frequency. The importance of timely and complete reporting needs greater emphasis in physician training programs. Targeted outreach to physicians has been shown to improve high quality reporting of adverse events.[32] Therefore, accurate and routine reporting could also be encouraged though direct communications from FDA and sponsors to physicians, health care providers and patients.

While more extensive and more accurate MedWatch reporting is essential for identification of adverse events, it must be accompanied by timely analysis of the received reports to ultimately ensure public health. **The number of reports received has been increasing each year and is now three times greater than a decade ago (*Figure 2*).** Congress must provide FDA with the resources for advanced information technology for improved systematic data collection and evaluation, as well as the necessary personnel to keep pace and provide expeditious and accurate analysis of the data.

> Congress must provide FDA with the resources to keep pace and provide expeditious and accurate analysis of the data.

3.2 Engage in public-private partnerships

While changes can be made to systematically advance drug safety monitoring in the future, reliable incidence data is needed now to ensure the safety of products that are already on the market. To utilize already established large clinical databases, FDA should establish public-private partnerships to aid in safety monitoring and data management. To obtain reliable incidence and outcome data, FDA should develop a Request for Proposals (RFP) for drug safety monitoring and

solicit proposals from appropriate networks or institutions that can provide long term safety monitoring for specific disease categories. Contractual use of such databases would provide valuable information regarding drugs that are already widely used. Furthermore, large-scale population databases like those established by Medicare or the Veterans

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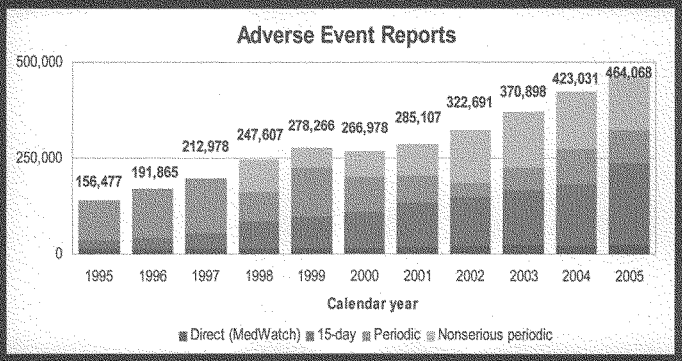
Administration Health System or private healthcare networks, such as Kaiser or UnitedHealth Group, might be used to continuously monitor particular conditions or treatment outcomes, as well as the occurrence of adverse events. While the use of these types of data may have limitations, such as limited or incomplete patient medical history or disease-specific focus, they could be used for hypothesis generation or create a framework for longitudinal data monitoring. International collaboration should also be encouraged. More often than ever before, new drugs are being introduced at the same time in the US and abroad. Partnerships that facilitate the access to information through an international collaboration would improve post-market surveillance among large, diverse populations.

Since many of these information systems are already established, the largest barrier would likely be the resources to support such a large-scale data mining program. In order to maintain an unbiased partnership, an equitable balance between public and private funding will be required for such an initiative. Associated costs would not likely be as burdensome as the resources that are currently put into the growing number of phase IV observational studies.[33] Accurate monitoring and evaluation of large user populations could also provide retrospective epidemiological information.[34] This would identify already existing data sets that phase IV studies are often designed to create and potentially mitigate the number of costly, time consuming post-marketing trials that are necessary. While a requirement of phase IV trials for all drugs would be inappropriate, enhanced post-marketing surveillance would not replace the need for all phase IV trials. Well-designed phase IV trials are often essential to establish clinical benefit following accelerated approvals, to perform dosing optimization, or to establish the causality of certain adverse events. Such partnerships would also not eliminate the need for other essential programs already in place by FDA and drug sponsors, as well as the extensive industry efforts of overall pharmacovigilance.

Additionally, Congress should permit FDA to participate in public-private partnerships that would enable the agency to receive philanthropic support for enhanced employee training and the support of research fellowships.

FIGURE 2



Source: CDER 2005 Report to the Nation. http://www.fda.gov/cder/reports/rtn/2005/rtn2005.htm Accessed 11/20/06.

3.3 Implement electronic medical records

Utilizing established data sources is important for the short-term future of post-market drug safety evaluation, but it is also important to examine other potential sources of information in the future. The implementation of electronic medical records would enhance the AERS and allow for widespread systematic tracking. The American Health Information Community (AHIC) is a forum of stakeholders that was established in order to advise the Secretary of Health and Human Services on the implementation and common interoperability framework for health IT.[35] The current initiative by AHIC to create a standard infrastructure of electronic health records should be supported by Congress. Such support is not only needed to continue the work done by AHIC but also to address challenges that will be faced by FDA and the medical community during the adaptation process. Furthermore, as the conversion to electronic medical records progresses, FDA itself should take steps to ensure that the agency is systematically and technologically prepared to utilize the benefits from streamlined recording.

Standard electronic health records should routinely include data related to the safety and efficacy of new treatments. In addition, recording data to capture patient reported symptoms and quality of life/functional status ratings would provide new data that is currently not available. Such information would allow for easier post-market follow-up of new therapies through the establishment of large-scale data sets. Such post-market reporting would be conducted by qualified healthcare providers, and would allow determination of different patient care requirements, resulting in the formation of a useful longitudinal response report that provides both benefit and risk data. Active surveillance would make it possible for FDA to identify, and ideally, recommend ways to manage serious side effects of new products, in the event that they are identified.

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A number of challenges arise when considering electronic records as a source of accurate information for efficacy and safety surveillance, such as linking records of various specialists that a patient may see. Nevertheless, as the progression to electronic records advances, there will be opportunities to conduct pilot programs that utilize electronic records as an additional data source.

3.4 Share funding for safety programs equitably

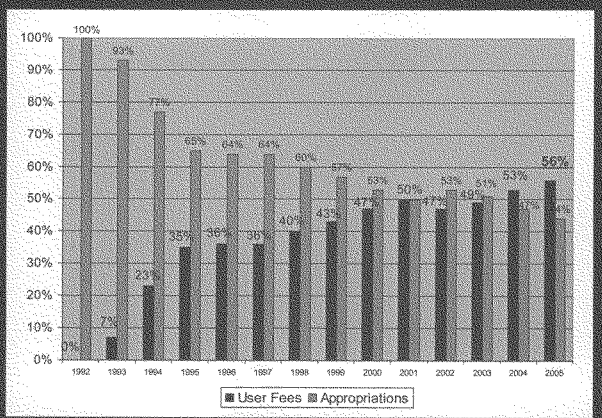
All of the above recommendations are designed to enhance drug safety by strengthening the programs that are already in place as well as utilizing IT advances and new public-private partnerships to establish new methods of data collection and review. Implementing and supporting advanced safety programs will require more funding for FDA. Funding for programs to ensure the safety and efficacy of new products should be equitably shared between public and private sources. In 1992, the Prescription Drug User Fee Act (PDUFA) was passed by Congress to authorize the FDA to collect fees from pharmaceutical and biotechnology companies to support the rising costs of drug review. The authorization of user fees was accompanied by the establishment of performance standards, including timelines, for FDA product review.[36] Since the initial establishment of PDUFA, new goals have been added and user fees have increased substantially,[37,38] a trend that is expected to continue.[39] In order to support the work load related to the FDA review process, the total funding of human drug review has increased over 225 percent since the original PDUFA authorization. However, **the rate of user fee increases has far surpassed the rate of increase of congressional appropriations *(Figure 3)*.**[40] Even with enhanced user fees, **the lack of funding has caused other programs at FDA to suffer in order to sustain the increasing cost and personnel for drug reviews *(Figure 4)*.**[41]

> Even with enhanced user fees, the lack of funding has caused other programs at FDA to suffer in order to sustain the increasing cost and personnel for drug reviews.

Insufficient funding for non-review associated programs subsequently reduces the number of available experts able to focus on other priority projects. For example, in 2003 the Infectious Disease Society of America requested that the guidelines being developed by FDA for new antibacterial drug development for five specific conditions be elevated to priority status.[42] While this is a scientifically challenging endeavor, FDA has not issued these guidance documents, in part, due to the lack of resources to devote to such programs. The completion of such guidance documents would be extremely valuable. These guidelines would permit any company filing for a sinusitis indication, one of the conditions for which a guidance document was requested, to know exactly what is required by the agency without the need to negotiate a different protocol for every drug. In the long run, it would save resources and help develop new, beneficial therapies faster.

It is clear that proper funding is essential to ensure efficient

FIGURE 3



Sources: http://www.fda.gov/oc/oms/ofm/budget/2005/BIB/APPL/services.htm. PDUFA Reports and Plans: http://www.fda.gov/oc/pdufa/reports.html Accessed 11/20/06

and accurate review. However, the agency must not rely solely on private funding. As industry has increasingly supported the cost of review programs, the public's confidence in the agency has diminished. Many today see the influence of the pharmaceutical and biotechnology industry as excessive.[43,44,45] For FDA to remain a review agency independent of industry and to avoid any appearance of lack of independence, it desperately needs additional congressionally-allocated resources. An increase in the level of federally appropriated funding will enhance overall FDA productivity and promote its continued success and improved perception of its independence among the general public. This can be accomplished by reconsidering the so-called "trigger" that requires only annual cost-of-living adjustments in direct FDA appropriations to continue to authorize user fee revenue. Unfortunately, this trigger has become a "ceiling" and not a "floor" for direct governmental appropriations to FDA. An additional mechanism needs to be designed that provides larger direct funding increases to support new incremental jurisdiction and need.

4. Advance current scientific opportunities to create a stronger, safer, science-based FDA

4.1 Increase support for the Critical Path Initiative

While identifying new methods of collecting and monitoring data are important, the entire FDA infrastructure must be prepared for technological advances. As science progresses and new treatments emerge from laboratories and clinics around the world, FDA must be equipped to perform accurate and efficient evaluation and continue its science-based tradition. It is imperative that resources be devoted to increase the support for the Critical Path Initiative to modernize FDA. In 2004, FDA released the Critical Path report to address potential methods to advance the drug development pipeline through the formation of an advanced scientific and technical tool kit.[46] Two years later, FDA released the Opportunities List which outlined seventy-six projects that would build this tool kit and speed the development and approval of medical products.[47] These seventy-six projects are distributed in six categories: biomarker and disease model development, streamlining clinical trials, harnessing bioinformatics, modernizing manufacturing, products for urgent public health needs, and developing therapies for pediatrics. Advancing the outlined projects would require a joint effort on the part of the public and private sector.

> Advancing the Critical Path Initiative will result in new ways to diagnose, treat, cure or prevent disease and allow life-saving therapies to reach patients faster while reducing the overall cost of healthcare in the country.

Congressional funding and researcher focus on the opportunities outlined by the Critical Path Initiative will lead to modernized drug development practices and overall

Percentage of FDA Funds Obligated for the Drug and Biologic Review Processes and for Other FDA Activities, Fiscal Years 1992 and 2000

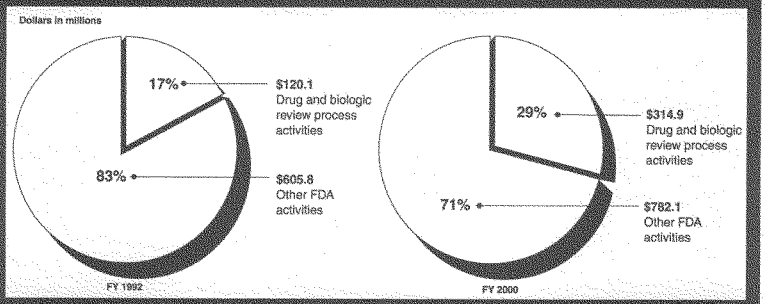


FIGURE 4

Note: Total FDA obligations were $725,887,020 in 1992 and $1,097,067,544 in 2000 and exclude rental payments to the General Services Administration and building and facilities expenditures.

Sources: FDA and GAO-02-978 PDUFA (See Fees http://www.gao.gov/new.items/d02978.pdf Accessed 11/6/06.

improvement of public health. Dr. Janet Woodcock, Deputy Commissioner for Operations at FDA, believes that the advancement of the Critical Path is "necessary to bring the promise of the new science to therapeutic reality."[48] A central goal of the Critical Path Initiative is to provide tools to identify patients who will most likely respond to particular treatments, thereby improving the risk to benefit ratio. If that can be accomplished, it should result in new ways to diagnose, treat, cure or prevent disease and allow life-saving therapies to reach patients faster while reducing the overall cost of healthcare in the country.

4.2 Prioritize discovery, evaluation and validation of new biomarkers

One specific area that has received a great deal of attention is the discovery of biological indicators, termed "biomarkers," that serve as a signal or measurement of a process, event, or condition. The establishment of new biomarkers to be used by scientists for drug discovery, manufacturers in development, and accepted by regulators during product evaluation will require collaboration from all stakeholders. In order to maximize resources and efficiency, public-private partnerships should be formed. Examples of such efforts include the biomarker consortium of FDA-NIH-CMS-PhRMA,[49] the Predictive Safety Testing Consortium at the Critical Path Institute,[50] and Clinical Research Information Exchange (CRIX) among NCI-FDA-PhRMA.[51]

While this field presents seemingly infinite opportunities, it is important to prioritize discovery of new biomarkers in order to efficiently improve drug evaluation and medical technology. In particular, new biomarkers that can improve safety are urgently needed. Active investigation in pharmacogenetics is underway to identify biomarkers that can explain, predict, and ultimately prevent adverse events. NIH initiatives and collaborative research partnerships should place high priority upon the identification and use of biomarkers to (1) determine the role of genetic polymorphisms in causing drug toxicities; (2) establish effective strategies for selecting patients for treatment with specific drugs and (3) identify early biomarkers of drug benefit. The sub-populations most susceptible to an adverse event could be identified by detecting the presence or absence of a biological indicator. In order to accomplish this, pilot studies of drug toxicity patterns in large, defined populations should include the collection of blood specimens and, where possible, tumor specimens to allow correlative studies of biomarkers to drug toxicity and response. Such efforts could capitalize upon other federally funded programs, such as the NCI-sponsored Early Detection Research Network (EDRN).[52]

CONCLUSION

FDA is the critical regulatory agency for new drugs and product safety. The assessment of benefits and risks must continue to occur simultaneously and not in separate, independent settings. In order for the agency to successfully continue to increase efficiency and productivity, the current system needs to be enhanced. While the agency's methods have recently faced criticism, FDA and its drug review and approval process is not broken. In fact, the percentages of FDA safety-based withdrawals have remained essentially the same over the years despite increased drug reviews and approvals and decreased review times established by PDUFA goals.[26] Nonetheless, at this juncture and in light of the current climate, strengthening FDA to ensure its continued success is necessary and will require a concerted effort on the part of all stakeholders.

First, increasing awareness and education can enhance public trust in the agency. Second, even though FDA has been a long-standing model for successful drug monitoring, the agency must be prepared to face future challenges and be supplied with the resources to confront them. Third, as scientific technology advances, FDA must have the trained staff and innovative tools to progress with it and routinely and automatically evaluate increased, accurate data. In order to accomplish this, FDA should enhance the existing infrastructure responsible for systematic safety monitoring and adverse event reporting. Furthermore, in addition to new methods of surveillance and data collection, new tools for evaluation are needed. Finally, support of the Critical Path Initiative and encouragement for public-private partnerships to enhance post-marketing surveillance is essential.

With proper advancement, support, and leadership, FDA can move into the twenty-first century and firmly remain the gold-standard of science-based drug review and safety monitoring.

FOOTNOTES

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COMMITTEE BIOGRAPHIES

CHAIR:

Robert C. Young, M.D.

President, Fox Chase Cancer Center
Philadelphia, PA

Robert C. Young, M.D., is president of Fox Chase Cancer Center in Philadelphia, which includes one of the nation's largest hospitals dedicated solely to cancer and the first such hospital in the country. He is internationally known for his work in the treatment of lymphoma and ovarian cancer. He is a past-president of the American Society of Clinical Oncology (ASCO), the American Cancer Society and the International Gynecologic Cancer Society.

Young received ASCO's Distinguished Service Award for Scientific Leadership in 2004 and was co-recipient of the 2002 Bristol-Myers Squibb Award for Distinguished Achievement in Cancer Research for his research in ovarian cancer.

A medical oncologist, Young is the author of more than 400 peer-reviewed publications. Based on the number of medical literature citations, he was one of the top 400 scientist-authors in the United States for 1980-1990, according to the Institute for Scientific Information. Young serves as chairman of the Board of Scientific Advisors of the National Cancer Institute. He is a former member of the National Cancer Policy Board at the Institute of Medicine and is past chairman of the board of the National Comprehensive Cancer Network, a nationwide alliance of 20 leading academic cancer centers dedicated to insuring the highest-quality, cost-effective cancer care.

A fellow of the American College of Physicians, Young is also a member of the prestigious American Society of Clinical Investigation. He has served on the subspecialty board on medical oncology for the American Board of Internal Medicine, on the experimental therapeutics study section of the National Cancer Institute and on the ovarian cancer implementation committee for the Department of Defense.

Young was an associate editor of the Journal of Clinical Oncology from 1987 to 2001 and is currently chairs the editorial board of Oncology Times. In 1995, he served as chairman of the General Motors Cancer Research Foundation's Charles F. Kettering Selections Committee.
Born in Columbus, Ohio, Young received his B.Sc. degree in zoology in 1960 from Ohio State University and his M.D. in 1965 from Cornell University Medical College. Following his internship at New York Hospital, he completed his residency at NCI and Yale-New Haven Medical Center. He is board-certified in internal medicine, hematology and oncology by the American Board of Internal Medicine.

MEMBERS:

Carolyn R. "Bo" Aldigé

President & Founder, Cancer Research and Prevention Foundation of America
Alexandria, VA

Carolyn R. ("Bo") Aldigé is president of the Cancer Research and Prevention Foundation, a national non-profit organization she founded in 1985 in memory of her father, Edward P. Richardson, who died of cancer one year earlier. In the 20 years since its inception, CRPF has provided more than $88 million in support of its mission: cancer prevention and early detection through research, education, community-based programs and advocacy, and has become nationally recognized as a leader in the fight against cancer through prevention.

In January 2006, Ms. Aldige completed a fourth two-year term as president of the National Coalition for Cancer Research, an organization which focuses it efforts on educating policymakers and the general public about the value of cancer research. She remains on the Coalition's board and also serves on boards of directors/advisors of seven National Cancer Institute-designated Comprehensive Cancer Centers and as a member of the board of five additional non-profit cancer-related organizations. She has been a member of C-Change (formerly the National Dialogue on Cancer) since its inception. She serves on several steering committees and task forces of the American Association for Cancer Research, American Society of Clinical Oncology, Coalition for a Stronger FDA, Global Lung Cancer Coalition and National Colorectal Cancer Roundtable. For her many contributions to the Washington, DC community, Carolyn Aldigé was named a Washingtonian of the Year 1996. In 2004, she received the American Association for Cancer Research Public Service Award in recognition of "significant and sustained contributions to the fight against cancer by individuals who work in the public arena." She was honored in 2005 by the American Society of Clinical Oncology, receiving the organization's highest award for public service. In 2006 she received the Distinguished Service Award from the American Society of Preventive Oncology. She is the only individual to have been honored by all three of these prestigious professional societies.

She is the recipient of many additional awards for her service to cancer research and contributions to the Washington, DC community, including the George Washington University Public Service Award, the Excellence Award of the AACR Associate Member Council; a Pioneer in Prevention Award presented by the National Cancer Institute; the Yetta Rosenberg Humanitarian Award from the Gloria Heyison Breast Cancer Foundation; the Belva Brissette Advocacy Award from the Breast Cancer Resource Committee and the Howard University Legacy of Leadership Award.

Carolyn Aldige is a graduate of Randolph-Macon Woman's College.

Diane Balma

Vice President, Public Policy, Susan G. Komen For The Cure
Dallas, TX

Diane Balma, a breast cancer survivor, joined the Susan G. Komen Breast Cancer Foundation in 1998, serving as Senior Counsel and Director of Public Policy. Her responsibilities include providing expert legal advice and counsel to members of Komen's Executive Team team, senior management, and leaders in the Affiliate network, which consists of more than 100,000 survivors and activists and 125 Affiliates across the United States, as well as in Puerto Rico, Germany and Italy. Balma works closely with Komen's staff, volunteers and the Board of Directors to fulfill the organization's promise to save lives and end breast cancer forever by Empowering people, Ensuring quality care for all and Energizing science to find the cures.

As Vice-President of Public Policy, Balma

manages legislative affairs and public policy activities between Washington, D.C. consultants and Komen executive management. She is nationally recognized for her expertise in matters regarding breast health care legislation.

In 1995, Balma was diagnosed with breast cancer at age 30. She subsequently became an advocate for cancer patients nationwide, specializing in employment discrimination and insurance coverage cases. Prior to joining Komen, Balma was in private practice in the San Francisco Bay Area from 1991 through 1996. A graduate of the University of the Pacific, Stockton, Calif., Balma received her J.D. from Pacific in 1991 with high honors.

John G. Bartlett, M.D.

Professor of Medicine, Division of Infectious Diseases, Department of Medicine, Johns Hopkins University School of Medicine
Baltimore, MD

John G. Bartlett, M.D. is a Professor of Medicine, Division of Infectious Diseases at Johns Hopkins University. Dr. Bartlett was chief of the Division of Infectious Diseases in the Department of Medicine at the Johns Hopkins University School of Medicine in Baltimore from 1980-2006 and founded the Johns Hopkins AIDS service in 1983.

Dr. Bartlett is a past president of the Infectious Diseases Society of America (IDSA) and chair of the Society's Task force on Antimicrobial availability. IDSA represents nearly 8,000 infectious diseases physicians and scientists devoted to patient care, education, research, and community health planning in infectious diseases. Members of the Society include experts in vaccine science, antiviral development, hospital epidemiology, and public health. The threat of pandemic influenza and availability of new antibiotics for resistant bacteria are issues of great concern to the Society. Dr. Bartlett was president of IDSA in 1999. Prior to becoming president, he served on the Society's Board of Directors and chaired the Infectious Diseases Training Directors Program Committee.

Dr. Bartlett earned his medical degree from Upstate Medical Center in Syracuse, N.Y., completed his internship at Peter Bent Brigham Hospital in Boston, senior residency at the University of Alabama in Birmingham, and his fellowship in infectious diseases at UCLA School of Medicine and Wadsworth VA Hospital in Los Angeles.

Dr. Bartlett's research interests include C. difficile-associated colitis, the protected brush catheter for pneumonia, the pathogenesis of intra-abdominal sepsis, anaerobic infections of the lung and clinical aspects of HIV infection. Other professional interests include guidelines (AIDS, community-acquired pneumonia, upper respiratory tract infections and bioterrorism), use of the Internet for infectious disease management and bioterrorism response. Dr. Bartlett is a member of the Institute of Medicine, a Master of the American College of Physicians, a recipient of the Kass Award of the IDSA and the 2005 winner of the Maxwell Finland Award of the NFID. He has authored more than 600 original articles and reviews, 260 book chapters and 61 books.

Edward Benz, Jr., M.D.

President, Dana-Farber Cancer Institute
Boston, MA

Dr. Benz is president of DFCI, CEO of Dana-Farber/Partners CancerCare, director and principal investigator of Dana-Farber/Harvard Cancer Center, and a member of the Governing Board of Dana-Farber/Children's Cancer Center. Dr. Benz is also a Richard and Susan Smith Professor of Medicine, Professor of Pediatrics, Professor of Pathology, Harvard Medical School. He is also a clinical hematologist and an active NIH-funded investigator. He is a past President of the American Association of Cancer Institutes (2005), an Elected Fellow of American Association for the Advancement of Science (2004), and a member of the Institute of Medicine (2004)

His laboratory continues to focus on the molecular pathology and physiology of red cell development, the molecular basis of inherited hemolytic anemias, and the use of the red cell homeostatic system as a model to study gene regulation and growth control in other tissues.

William P. Bro

President and Chief Executive Officer, Kidney Cancer Association
Evanston, IL

President and Chief Executive Officer of the Kidney Cancer Association (KCA), a global voluntary health organization, Mr. Bro is an honors graduate, University of Phoenix, B.S. in Business Management and a Nonprofit Executive Scholar, Kellogg School of Management, Northwestern University. He is a retired corporate executive, with three decades of experience in broadcast station ownership, aviation services management, communications consulting, and website development. He is past chairman of the KCA, succeeding the organization's late founder, Eugene P. Schonfeld, in 1997, and serving as its CEO since 2002. Mr. Bro is a member of the National Cancer Institute Director's Consumer Liaison Group (DCLG), Cancer Leadership Council, National Health Council, National Coalition for Cancer Research, Association Forum of Chicagoland, and the Nonprofit Financial Center. He is a director of Friends of Cancer Research, Washington, D.C. Mr. Bro also holds a seat on the Kidney Health Council of the American Urological Association (AUA), and is listed as co-author of a recent journal article on renal cell carcinoma.

The KCA reaches 72,000 constituents in Canada, the United States, the European Union and more than 100 other countries from its suburban Chicago offices. The organization's annual budget is approximately $1.2M, and it employs a fulltime staff of only four people, with a governing board of eight members, and a volunteer medical advisory board of more than thirty world-renowned cancer specialists and biostatisticians. The KCA's mission is the global eradication of death and suffering from kidney cancer. Mr. Bro is a sixteen-year kidney cancer survivor whose avocation is flying; he is an instrument-rated commercial pilot.

Michael A. Caligiuri, M.D.

Director, Comprehensive Cancer Center The Ohio State University James Cancer Hospital & Solove Research Institute
Columbus, OH

In July 2003, Dr. Caligiuri, a medical scientist who has conducted extensive research in leukemia, lymphoma and immunology, was named director of the OSU Comprehensive Cancer Center (OSUCCC) and deputy director of The James Cancer Hospital and Solove Research Institute. He also chairs the Division of Hematology and Oncology in the OSU College of Medicine and Public Health, Department of Internal Medicine. In addition, he is a professor of medicine and a Distinguished University Scholar who holds the John L. Marakas Nationwide Insurance Enterprise Foundation Chair in Cancer Research. Caligiuri's laboratory, which has nearly 40 members, focuses on research in leukemia, lymphoma and the human immune system. His current projects include developing a vaccine to prevent lymphoma in organ transplant patients and working to target genetic defects in leukemia and lymphoma for curative therapies. Research efforts led by Caligiuri at OSU have received more than $20 million from the National Cancer Institute, including a $9.5 million program project grant to study immunity in cancer. Caligiuri earned his graduate and medical degrees at Stanford University School of Medicine, then trained in internal medicine, oncology, bone marrow transplantation and immunology at Harvard before joining the Harvard Medical School faculty in 1989. He later went to Roswell Park Medical Center in Buffalo, NY, and was recruited to the OSUCCC in 1997 as associate director for clinical research. He has more than 130 publications in scientific journals.

Bruce A. Chabner, M.D.

Clinical Director Massachusetts General Hospital Cancer Center
Boston, MA

Dr. Bruce Chabner is the Clinical Director of the Massachusetts General Hospital. His main fields of research focus on the biochemistry and pharmacology of folate antagonists, experimental therapeutics, and clinical trial design. He serves as the Associate Director of Clinical Science at Dana Farber/Harvard Cancer Center and has held numerous other academic appointments including Chief of Hematology/Oncology at Massachusetts General Hospital, Professor of Medicine at Harvard Medical School, and Director of the Division of Cancer Treatment of the National Cancer Institute from 1982 to 1995. Dr. Chabner received his B.A., summa

cum laude, from Yale College (1961) and an M.D., cum laude, from Harvard Medical School (1965). Over the years, Dr. Chabner has received numerous awards, including the Karnofsky Award of the American Society for Clinical Oncology, the Bruce F. Cain Award for Drug Development of the American Association for Cancer Research, and the Public Health Service's Distinguished Service Medal.

William S. Dalton, M.D., Ph.D.

CEO & Director, H. Lee Moffitt Cancer Center & Research Institute
Tampa, FL

Dr. Dalton has served as CEO and Director of the H. Lee Moffitt Cancer Center & Research Institute since 2002. In addition to holding a Ph.D. in Toxicology and Medical Life Sciences, Dr. Dalton is a physician, board certified in both Internal Medicine and Medical Oncology. He was the Founding Director of the Bone Marrow Transplant Program at the University of Arizona, and from 1997-2001 he was both Deputy Director of the Moffitt Cancer Center, and the Chairman of the Department of Interdisciplinary Oncology at the University of South Florida. He served as Dean of the College of Medicine at the University of Arizona in Tucson from 2001-2002. Over the course of two decades in cancer research Dr. Dalton has authored or co-authored numerous articles, and has served on numerous editorial boards. He is an expert in the biology and treatment of multiple myeloma.

Dr. Dalton's research examines the influence of the tumor microenvironment on tumor cell survival and progression. His research has demonstrated that the tumor microenvironment provides a sanctuary for subpopulations of tumor cells to evade or circumvent drug-induced death and that this may represent a form of de novo drug resistance. Furthermore, this extrinsic form of de novo drug resistance contributes to minimal residual disease, resulting in emergence of acquired drug resistance. Dr. Dalton and his colleagues have found that elements of the bone marrow microenvironment, including extracellular matrices and normal stromal elements, protect hematologic malignant cells from drug-induced cell death.

Nancy Davenport-Ennis

Chief Executive Officer
National Patient Advocate Foundation and Patient Advocate Foundation
Washington, DC

Nancy Davenport-Ennis, cancer survivor, is the Founder and Chief Executive Officer of two organizations founded in 1996, National Patient Advocate Foundation (NPAF), a policy organization, headquartered in Washington, DC that seeks to improve access to care through regulatory and policy initiatives at the state and federal levels and Patient Advocate Foundation (PAF), a 501(c) 3 direct patient services non-profit organization, headquartered in Newport News, VA, providing professional case management services in order to resolve patient access issues. PAF served over 6 million contacts in the FY2005/2006.

Davenport-Ennis has been appointed to, and currently serves on, several national committees including and appointment by the United States Secretary of Health and Human Services as a Commissioner on the American Health Information Community (AHIC) with Health and Human Services (HHS) serving as Co-Chair of the Consumer Empowerment Working Group for AHIC, Directors Consumer Liaison Group (DCLG) with the National Cancer Institute (NCI), a voting seat on the Medicare Coverage Advisory Committee (MCAC) at Centers for Medicare and Medicaid Services, Access to Quality Cancer Care Team, a committee of C-Change, One Voice Against Cancer, Virginia Governor's Government & Regulatory Reform Task Force, Virginia Attorney General's Regulatory and Government Reform Task Force-Healthcare Working Group, Health Information Technology Council for Virginia and the Mayor's Committee on Medicaid and Physician Recruitment in Newport News, VA. She also serves on the Board of Directors for Friends of Cancer Research, the Advisory Board for the Intercultural Cancer Council, external Board of Review for the Siteman Cancer Center in St. Louis, MO, the PRR Advisory Board for Oncology Times, In-Touch, Coping and Managed Care and Cancer magazines. She has served as a Congressional witness before the Senate and House committees addressing access issues confronting patients.

Throughout her career in patient advocacy, Davenport-Ennis' expertise has been sought by national and local media outlets for articles addressing access issues confronting patients reflecting the value of case management and/or legal interventions. Articles have appeared in The Wall Street Journal, New York Times, US News and World Report, USA Today, Washington Post, The Boston Globe; Houston Chronicle, The Daily Press, The Virginian Pilot , Inside CMS, Family Circle Magazine; Parade Magazine, Readers Digest; Prevention Magazine, Self Magazine, All You, Real Simple Magazine, Glamour Magazine, Nursing Spectrum, Business Week, Hematology Oncology Times, Physicians Practice Magazine, Coping Magazine, Women and Cancer, American Family Physician Monograph on Cancer, NBC Nightly News, Good Morning America, CBS affiliate stations, and the Lifetime Network

Ms. Davenport-Ennis is the recipient of the 1989 Outstanding Young Woman of America Award, the Association of Community Cancer Centers Advocate of the Year Award and the U.S. Oncology Medal of Honor Award. Ms. Davenport-Ennis was also appointed to the Governor's Commission on the Uninsured in Virginia. Davenport-Ennis was also named as a Paul Harris Fellow by the National Rotary Foundation. Davenport-Ennis holds a B.A. degree in English from Campbell University. She resides in Yorktown, Virginia with her husband, John H. Ennis, Jr. and has two daughters and four grandchildren.

Michael A. Friedman, M.D.

President & CEO, City of Hope
Duarte, CA

Before becoming the President and CEO of City of Hope in 2003, Dr. Friedman held a number of top-level appointments with some of the country's most important health care organizations. He spent nearly a decade at the University of California at San Francisco Medical Center, serving as an associate professor of medicine.

In 1983, he moved to the NCI and later became associate director of the Division's Cancer Therapy Evaluation Program.

He was recruited to serve as FDA deputy commissioner and tapped by President Clinton to serve as acting commissioner of the agency. Friedman is credited with helping to streamline the FDA's approval process and for spearheading the highest level of approvals for products, devices and food ingredients in a four-year period.

Friedman's career also includes the position of senior vice president of Clinical Affairs for Searle/Monsanto and senior vice president for Medical and Public Policy for Pharmacia Corporation. He has received numerous awards, including the 1999 Surgeon General's Medallion, the American Cancer Society Faculty Research Award and the PHS Distinguished Service Medal. Friedman is certified by both the American Board of Internal Medicine and the Subspecialty Board of Medical Oncology.

William N. Hait, M.D., Ph.D.

Director, The Cancer Institute of New Jersey
New Brunswick, NJ

Dr. Hait has been Director of The Cancer Institute of New Jersey and Professor of Medicine and Pharmacology and Associate Dean for Oncology Programs at the University of Medicine and Dentistry of New Jersey (UMDNJ)–Robert Wood Johnson Medical School since January 1993. Dr. Hait received his M.D. and Ph.D. (Pharmacology) degrees from the Medical College of Pennsylvania. He joined the Yale University School of Medicine faculty in 1984 and was promoted to Associate Professor of Medicine and Pharmacology.

Dr. Hait is currently the President elect of the American Association for Cancer Research (AACR). Beginning March 19, 2007, he will be joining Johnson & Johnson as Senior Vice President and Worldwide Head of Hematology/ Oncology Research and Development.

Dr. Hait served as Associate Director of the Yale University Comprehensive Cancer Center and Director of the Breast Cancer Unit and Co-Director of the Lung Cancer Unit at the Yale University School of Medicine. He was appointed Chief of Medical Oncology at the Yale University School of Medicine in 1988. Dr. Hait is a prolific author with more than 200 articles, chapters, and abstracts to his credit.

The longest interest in the laboratory has been in signal transduction systems that are altered in malignancy. His laboratory

has identified an inhibitor of the kinase (Cell Growth and Differentiation 8:327-334, 1997), which will form the basis of a drug discovery program to determine whether inhibition of calmodulin kinase will be a viable approach to the treatment of certain cancers. The second area of interest is the genetic determinants of sensitivity to cancer chemotherapy. His laboratory was instrumental in the quest for discovering drugs that inhibit the function of the mdr1 gene product, P-glycoprotein

G. Denman Hammond, M.D.

Founder & Trustee, National Childhood Cancer Foundation
Arcadia, CA

Dr. Hammond began treating children with cancer using experimental chemotherapy in 1952 and joined the first NCI cooperative chemotherapy research group in 1957. When elected Chair of the Group in 1968, he reorganized and enlarged its mission from chemotherapy for acute leukemia to a multi-disciplinary group including surgeons, radiation oncologists, pathologists and basic scientists in order to provide comprehensive care for children with solid tumors as well as leukemias.

During his nearly 25-year term as national Chairman of the Children's Cancer Group (CCG), the Group grew to include more than 2,000 specialists and 120 North American member institutions, in conducting clinical and laboratory research on all types of childhood cancers. Multi-disciplinary team work in research and care became the national standard for children and adolescents with cancer.

Dr. Hammond was the Founding Director of the Comprehensive Cancer Center of the University of Southern California from 1971 to 1981 and developed the USC-Norris Cancer Hospital, the first free-standing cancer hospital on the west coast. He later served as Associate Vice President for Health Affairs. In 1989, Dr. Hammond envisioned and founded the National Childhood Cancer Foundation to raise public awareness and funds for national cooperation in research on childhood cancer. In 2000, the CCG merged with other NCI supported childhood cancer study groups to form the Children's Oncology Group (COG), the world's largest pediatric oncology research organization.

Today, Dr. Hammond continues to serve on the Board of Trustees and as a volunteer for the National Childhood Cancer Foundation. He is Emeritus Professor of Pediatrics at the University of Southern California and Children's Hospital Los Angeles.

Paul J. Limburg, M.D., M.P.H.

Associate Professor of Medicine, Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine
Rochester, MN

Dr. Paul Limburg is an Associate Professor of Medicine, Mayo Clinic College of Medicine and is a consultant in the Division of Gastroenterology and Hepatology, Department of Internal Medicine. He is also the Director for the Gastrointestinal Neoplasia Clinic and Principal Investigator for the multi-center Cancer Prevention Network. Dr. Limburg's research interests are primarily focused on molecular epidemiology of colorectal cancer; cancer chemoprevention; and the early detection of gastrointestinal cancers.

He earned his medical degree from the Mayo Clinic College of Medicine with a residency focus of Internal Medicine and a fellowship in Gastroenterology. In addition to his fellowship at Mayo Clinic, Dr. Limburg completed an advanced fellowship in Cancer Prevention at the National Cancer Institute. Dr. Limburg also received a master of public health degree from the Johns Hopkins School of Hygiene and Public Health. His work on community-based projects for cancer prevention earned him a Laurel Award from the Cancer Research and Prevention Foundation in 2005.

Scott Lippman, M.D.

Chair, Department of Clinical Cancer Prevention, M.D. Anderson Cancer Center
Houston, Texas

Dr Lippman's research interests cover the full spectrum of preclinical development (molecular mechanisms and targets) and clinical development (phase I, II, and III trials) of chemopreventive agents. He is the principal investigator for several NCI translational chemoprevention grants, the NCI Phase I and II Chemopreventive Master Agreements, the Clinical Cancer Prevention Program of the Cancer Center Support Grant, and major phase III NCI Intergroup prostate and lung trials.

Molecular targets are a major focus of current research, studying the biology of carcinogenesis and targets and mechanisms for promising chemopreventive agents. His recent primary publications report the first in vitro overall and mechanistic findings on the effects of selenium in inhibiting differential growth and inducing apoptosis in a comprehensive panel of malignant and normal prostate cells, profound IFN-signaling defects in squamous cell skin carcinogenesis, and novel molecular targets that mediate apoptosis induced by nonsteroidal anti-inflammatory drugs.

Recent phase III research includes work on 3 major national trials. Dr Lippman is the National Study Chair for the phase III NCI Intergroup trial of isotretinoin in preventing second primary tumors in more than 1,100 randomized patients diagnosed with stage I non-small cell lung cancer. This trial has contributed seminal findings on the natural history and biology of retinoid activity in tobacco-related lung carcinogenesis. He is also a part of the national leadership group of the Southwest Oncology Group/Intergroup Selenium and Vitamin E Cancer Prevention Trial to prevent prostate cancer in 32,400 men. This study is the largest cancer chemoprevention trial ever conducted. He also serves on the National Steering Committee of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene, which involves 22,000 women.

H. Kim Lyerly, M.D.

Director, Duke Comprehensive Cancer Center
Durham, NC

H. Kim Lyerly, MD, was appointed director of the Duke Comprehensive Cancer Center in 2003. The George Barth Geller Professor for Research in Cancer and an experienced surgical oncologist, Lyerly also holds faculty appointments in Duke's pathology and immunology departments. As director of the Duke Comprehensive Cancer Center, he is working to create the nation's best environment for bringing scientific discoveries rapidly into clinical practice

Dr. Lyerly is well known for his innovation in bringing basic science concepts into clinical testing and was part of the team of investigators who first reported the use of AZT for the treatment of HIV infection. He developed strategies targeting virally associated tumors with viral-specific immune cells and was the first to show this approach to be effective in eradicating tumors in mice, a technique that is now in clinical practice. He was a pioneer in the clinical testing of gene therapies for breast cancer, colon cancer, lung cancer and pancreatic cancer. For this work, he has been awarded peer-reviewed funding from the National Cancer Institute for the past 10 years.

John L. Marshall, M.D.

Chief, Division of Hematology/ Oncology Lombardi Comprehensive Cancer Center Georgetown University
Washington, D.C.

Dr. John Marshall is the Director of Developmental Therapeutics and GI oncology at the Lombardi Cancer Center of Georgetown University. He serves the cancer center as the Associate Director for Clinical Research, Director of Developmental Therapeutics and GI Oncology, and Director for Extramural Research. Dr. Marshall is focused on early phase clinical research for cancer patients. He has established an enduring productive record of innovative phase I and II clinical trials.

In the past 6 years, he has completed more than 40 phase I trials, 22 of which were first trials in human studies. These trials have centered around the testing of novel agents targeting PKC, angiogeneic factors, bcl-2, retinoid receptors, matrix metalloproteinases, and other novel targets. His current efforts are centered on the development of novel CEA-based vaccines to be used as therapeutics for cancer patients. The clinical research emphasizes translational endpoints performed in his laboratory and with collaborators and has been a hallmark of Dr. Marshall's published work. As part of this research, Dr. Marshall directs a clinical research training program.

The second major focus is on phase II and III clinical research in GI cancers. Dr. Marshall has lead 3 national trials in colon and pancreas cancer, and currently is the co-PI of a 900 patient international trial which will establish the new standard of care for the treatment of metastatic colon cancer He is a graduate of The University of Louisville School of Medicine and completed his specialty training in oncology at Georgetown.

Kathi H. Mooney, Ph. D., R.N.

Professor, University of Utah College of Nursing
Salt Lake City, UT

Kathi Mooney is a Professor at the University of Utah College of Nursing. Her research interests include cancer symptom management and outcomes of supportive care. She has published numerous book chapters and journal articles and is a frequent speaker on topics related to cancer symptom management, quality cancer care, oncology nursing and leadership.
Dr. Mooney is a past President of the Oncology Nursing Society. She is active in several cancer-related health policy and research advocacy groups. She is a member of the National Research and Medical Affairs Committee of the American Cancer Society and on the Board of Directors of the National Coalition for Cancer Research.

Currently she is the Principal Investigator of 3 separate multisite studies examining outcomes of oncology nursing practice, symptom patterns of neutropenic patients receiving cancer chemotherapy, and utility of a computer-based telephone home monitoring system to assist women with breast cancer to monitor and utilize self-care strategies for symptom management. A fourth study evaluating the same telephone system in improving provider-patient communication and symptom assessment is pending funding.

Jerrold M. Olefsky, M.D.,

Associate Dean for Scientific Affairs, University of California San Diego School of Medicine
La Jolla, CA

Dr. Olefsky is also a professor of medicine and Co-Chair of the Division of Endocrinology & Metabolism at the University of California, San Diego School of Medicine. He is a member of numerous professional societies including the American Society for Clinical Investigation, the American Diabetes Association, the Endocrine Society, the American Association for the Advancement of Sciences, and recently served as President of the Association of American Physicians. Dr. Olefsky serves on the editorial board for a number of professional journals and has over 400 peer reviewed publications.

His research program is divided into clinical investigation and basic research components. Clinical investigation approaches include studies aimed at identifying in vivo mechanisms underlying the pathogenesis of non-insulin dependent diabetes mellitus, obesity, and other disorders of insulin resistance. Studies are in progress to identify the relative role of each organ system (muscle, liver and fat) to the pathophysiology of NIDDM. In addition, a number of protocols are underway exploring new modes of therapy for established NIDDM as well as means of primary prevention for this disease. A major focus for the basic research program is to understand the molecular and cellular mechanisms of insulin and IGF-I action.

Richard L. Schilsky, M.D.

Associate Dean for Clinical Research, University of Chicago Pritzker School of Medicine
Chicago, IL

Dr. Schilsky earned his M.D. at the University of Chicago Pritzker School of Medicine in 1975. Following a residency in Internal Medicine at the University of Texas Southwestern Medical Center and Parkland Memorial Hospital, he received training in Medical Oncology and Clinical Pharmacology at the National Cancer Institute from 1977 to 1981. He then served as Assistant Professor of Medicine at the University of Missouri-Columbia School of Medicine from 1981-1984 when he returned to the University of Chicago.

An international expert in gastrointestinal malignancies and cancer pharmacology, he has served on a number of peer review and advisory committees for the NCI and previously served as Chair of the Oncologic Drugs Advisory Committee for the FDA. Dr. Schilsky currently serves as a member of the NCI Board of Scientific Advisors and recently completed a term as a member of the Board of Directors of the American Society of Clinical Oncology (ASCO). Dr. Schilsky has also been elected to be President of ASCO for 2008-2009. Since 1995, Dr. Schilsky has served as Chairman of the Cancer and Leukemia Group B.

He is a member of the external advisory committees of several comprehensive cancer centers including the Roswell Park Cancer Center, the Mayo Cancer Center, the MD Anderson Cancer Center and the Fred Hutchinson Cancer Research Center. He has also served as a member of the Selection Committee for the Bristol-Myers Squibb Award for Distinguished Achievement in Cancer Research. Dr. Schilsky is an Associate Editor of Clinical Cancer Research and Cancer and a member of the editorial board of Seminars in Oncology, the Journal of Cancer Research and Clinical Oncology and several other journals. He has published more than 225 articles and book chapters in the medical literature and is the editor of 4 books.

Ellen V. Sigal, Ph.D.

Founder and Chairperson, Friends of Cancer Research
Washington, DC

Friends of Cancer Research (Friends), a Washington, DC based non-profit organization, is dedicated to accelerating the nation's progress toward prevention and treatment of cancer by mobilizing public support for cancer research funding and providing education on key public policy issues.

Dr. Sigal serves on the National Cancer Institute Board of Scientific Advisors, the National Institutes of Health Foundation Board chairing its Public-Private Initiatives Committee, the American Association for Cancer Research Foundation Board, the Johns Hopkins Cancer Center Advisory Council, the Duke University Cancer Center Board of Overseers, and the Howard University Cancer Center Board of Visitors.

She served on the National Institutes of Health prestigious Director's Council of Public Representatives from 2003-2006. She was a Presidential Appointee to the National Cancer Advisory Board from 1992-1998 chairing its Budget and Planning Committee which oversees the federal cancer budget. She is a past member of the American Society of Clinical Oncology Foundation Board.

Dr. Sigal was honored in 2004 by the Association of American Cancer Institutes, ResearchAmerica, George Washington University Cancer Institute, International Spirit of Life Foundation, and Washingtonian magazine as a 2004 Washingtonian of the Year. In 2002 she received the American Society of Clinical Oncology Special Recognition Award, in 1999 the Sidney Kimmel Cancer Center National Leadership Award, and in 1998 the American Association for Cancer Research National Leadership Award.

Jerome W. Yates, M.D., M.P.H.

National Vice President for Research, American Cancer Society
Atlanta, GA

Prior to this appointment, Dr. Yates was senior vice president for population sciences and senior vice president for clinical affairs at Roswell Park Cancer Institute in Buffalo, New York.
Earlier, Yates served as the associate director for centers and community oncology at the National Cancer Institute (NCI) where he was part of the group responsible for the generation and subsequent evaluation of the Community Clinical Oncology Program (CCOP). He was also a participant in the NCI-funded research on aspects of supportive care and cancer in the elderly.

Much of Yates's early career included the intensive treatment of adults with acute leukemia and the protection of bone marrow transplant patients from infection using special patient isolators. These early research efforts led to the "7+3" treatment for acute adult leukemia that has been the standard therapy for acute myelocytic leukemia for many years.

Yates has been an active ACS volunteer in western New York, northwestern Pennsylvania, Ohio, and Vermont. His work with local and state committees led to the National Hospice Study, which demonstrated better quality of life for those terminal patients who were supported at home rather than in institutions.