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REAUTHORIZATION OF THE PRESCRIPTION DRUG USER FEE ACT

HEARING

BEFORE THE

SUBCOMMITTEE ON HEALTH

OF THE

COMMITTEE ON ENERGY AND COMMERCE

HOUSE OF REPRESENTATIVES

ONE HUNDRED TENTH CONGRESS

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REAUTHORIZATION OF THE PRESCRIPTION DRUG USER FEE ACT

TUESDAY, APRIL 17, 2007

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

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

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

Also present: Representatives Markey and Stupak.

Staff present: John Ford, Jack Maniko, Virgil Miller, Bobby Clark, Brin Frazier, Chad Grant, Ryan Long, Nandan Kenkermath, Jesse Levine.

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

Mr. PALLONE. I would like to call the meeting to order. And today we have a hearing on Reauthorization of the Prescription Drug User Fee Act. I recognize myself for an opening statement.

I would like to initially welcome everyone to today's hearing, which will be the first in a series of hearings over the next few weeks that will focus on issues involving the Food and Drug Administration, including the Medical Device User Fee and Modernization Act reauthorization, creating a pathway for FDA approval of follow-on biologics, as well as drug safety issues. But today's hearing will focus on the reauthorization of the Prescription Drug User Fee Act, otherwise known as PDUFA. Originally authorized in 1992, PDUFA has provided FDA with the additional resources it needs to efficiently review an application for a new drug or biologic to enter the market.

Prior to the 1992 law, it would take FDA up to 29 months, sometimes longer, to approve a new drug application or a biologic licensing agreement. This backlog was cause for concern for both patients and drug manufacturers. Patients had to wait longer to receive new therapies for life threatening illnesses, such as HIV/AIDS or cancer. Pharmaceutical companies were threatened by the loss of time they would have to recoup their investments on research and development.

In order to remedy these problems, Congress passed landmark legislation which established a user fee system in which drug manufacturers would provide a revenue source to the FDA to help expedite the review of new drug and biologic applications. Since its enactment, the user fee program has been viewed largely as a success. It has allowed FDA to increase the size of its work force in order to speed up review times. As a result, the median time between when a new drug application or biologic licensing agreement is submitted, and FDA approval has decreased dramatically.

But shorter review time should not be the only measure of success for the program. As we set out to reauthorize this important program for a third time, we must examine a number of issues that remain unresolved. For example, we must pay attention to the trade-offs we make by expediting FDA's approval process. There are legitimate concerns, both in and outside of Congress, that in our rush to speed drugs to market, we could be overlooking critical safety issues and place patients at risk. We must strike the right balance between a timely pre-market review process and a robust post-market surveillance system to ensure patients have access to the safest and most effective medicines.

Previous reauthorizations of PDUFA have focused more on the pre-market side of the process and I believe it is necessary for us to spend more time examining how we should strengthen our Nation's post-market surveillance system this time around. Now, to that end, the agreement reached between the FDA and industry to increase the amount of user fees that can go towards post-market surveillance is certainly a step in the right direction, but that is not to say that Congress should not take any steps further.

There are a number of proposals that would improve upon the FDA's ability to monitor a drug over the course of its life cycle, as the Institute of Medicine has suggested. We need to ensure that FDA has the resources and the authority necessary to ensure the safety of a drug once it is already on the market. And these are important issues that are quite literally life and death for millions of Americans; that is why this subcommittee will examine drug safety, in part, today but more thoroughly in a separate hearing, as well. We will have a separate hearing on drug safety, in general.

Furthermore, while I am pleased to see that the FDA and the industry have reached an agreement on direct-to-consumer advertising, I am not certain that what has been laid out will suffice. Under current law, FDA does not have prior approval authority for prescription drug use advertising. Rather, FDA relies on drug markets, drug makers, to voluntarily submit their ads to review. Nothing in the current proposal would change that and the program outlined in PDUFA still relies on the industry to voluntarily subject its ads to FDA review. This type of self-policing strikes me as something along the lines of the fox guarding the hen house and I realize that there are constitutional or first amendment concerns involved here, but this part of the proposal may need some work, particularly as it relates to the mass marketing of new drugs approved by the FDA.

In the end, I will say that many of us probably wish that there wasn't a need for the PDUFA program and that FDA could be funded entirely out of general revenues, but that possibility does

not currently exist. In the absence of that, I think that the PDUFA program has worked well and there is strong support for its reauthorization on a bipartisan basis and that we will obviously get more information about a number of these issues as we proceed today and the next few weeks.

I would like to thank our witnesses for being here today and I look forward to their testimony and I would now recognize our ranking member, Mr. Deal, for 5 minutes for the purpose of delivering his opening statement. Thank you.

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

Mr. DEAL. Thank you, Mr. Chairman. I want to thank you for giving the committee an opportunity to examine this important piece of legislation. PDUFA has helped the FDA evaluate new drugs in a timely fashion and has given patients faster access to approve medications. I am sure our witnesses today will testify of the many successes of PDUFA, but also to the need for changes during this round of reauthorization to ensure that program remains effective into the future.

Since the last authorization of PDUFA, new areas of concerns have arisen and I am certain the committee will fairly evaluate ways to improve the program as we move forward. For instance, I have been concerned, for a very long time, about the types of advertisements presented to consumers during recent years and I am pleased to see that PDUFA IV, before us today, addresses this area of direct-to-consumer advertising.

While I realize the industry has taken steps to ensure consumers are provided with accurate information, the establishment of a separate fee program for FDA review of these ads help solidify the FDA's advisory role. Hopefully, companies will take advantage of the opportunity to receive feedback on their television ads and that this will prevent patients from being misled by persuasive commercials. Today's patients are bombarded with information about how best to manage their health and they should be assured that this information is accurate.

The increased emphasis on post-market drug safety is also well placed. As the FDA receives information about adverse effects, they need the tools to evaluate these reports and quickly detect problems with approved medications. Allowing the FDA to continue to monitor the safety of the drug throughout its life and providing increased resources to improve the FDA's post-market safety efforts helps ensure that the drugs available to consumers are safe and effective.

The original PDUFA legislation marked a dramatic change in how the FDA funds its drug review activities to the point that today's user fees comprise a sizable portion of the FDA's budget. The committee should continue to monitor this dynamic that is created between the FDA and the industry and the original intent that user fees only supplement FDA's appropriations from Congress. Indeed, a variety of drug and FDA issues await action before this committee and I look forward to the testimony of the witnesses who will help inform us on our reauthorization efforts.

Mr. Chairman, I will yield back the balance of my time.

Mr. PALLONE. Thank you and recognize Mr. Waxman for an opening statement.

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

Mr. WAXMAN. Thank you very much, Mr. Chairman. Our hearing today is on reauthorization of PDUFA, Prescription Drug User Fee bill. This reauthorization also gives us an opportunity to look at other ways we can enhance FDA's ability to do its job. For example, by giving FDA the authority to approve bio-generics and enhancing its ongoing authority to see to it that drugs are tested on children. But perhaps, most importantly, the reauthorization of PDUFA will allow us to address the critical issue of drug safety.

Today, the confidence Americans have long held in FDA has been seriously shaken. I don't need to repeat the list of recent high-profile drug safety crises that led to this decline in confidence. FDA's drug safety program is in serious need of repair. The Institute of Medicine issued a high-profile report on drug safety, concluding (1) that our drug safety system is seriously dysfunctional, and (2) FDA cannot protect Americans from unsafe drugs unless Congress provides more resources and more legal authorities.

FDA currently lacks several critical authorities. FDA lacks authority to require post-market safety studies, even when necessary to determine a drug's risks. FDA lacks authority to impose necessary restrictions on the distribution of drugs shown to have risks. FDA doesn't have the ability to place controls on huge advertising campaigns at the launch of new drugs, which cause excessive use of drugs before their safety profile is clear. And finally, the agency's authority to require labeling changes after approval under the current system is so weak it guarantees the drug companies will be able to delay and water down needed warnings on drugs. We simply must address this problem.

There are some positive aspects of the negotiated FDA PDUFA package; it increases the amount of user fee dollars dedicated to post-market drug safety activities, but the proposal does nothing to give FDA the vitally important authorities it needs to protect the American public from risky drugs. That is why I hope that we can incorporate the bill that I have introduced with Representative Markey in this legislation, just as the Enzi-Kennedy drug safety legislation is being added to the PDUFA reauthorization in the other body.

This reauthorization will give us a rare but critical opportunity to take up this legislation and see it enacted. PDUFA has now become an entrenched feature of FDA's drug regulatory system, but it has not been without cost. Many people think that the stringent deadlines, timelines for taking action on new drug applications may lead to safety problems once they are on the market. Heavy reliance on user fees gives a suspicion that FDA is in the pocket of the pharmaceutical industry. A better balance between the amount FDA receives in user fees and the amount it receives in Federal dollars will help move us quite a way from dealing with this problem.

Thank you, Mr. Chairman, for holding this hearing.

Mr. PALLONE. Thank you, Mr. Waxman. The gentlewoman from New Mexico.

OPENING STATEMENT OF HON. HEATHER WILSON, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW MEXICO

Mrs. WILSON. Thank you, Mr. Chairman. I don't think there is any disagreement on this committee or in the members of the public that the prescription drug user fee has helped to speed the approval of lifesaving prescriptions. It has brought about $270 million of revenue into the FDA, allowing them to hire more people and has reduced the amount of time it takes to get a drug approved, from about 29 months down to 14 months. That is a tremendous accomplishment for this program and I think it needs to be reauthorized.

As we look at these balances between safety and access, I hope that we don't overemphasize or don't wrongly emphasize what might be a false public perception that my colleague from California just mentioned and that we focus on the things that matters, as public servants, and that is safety and rapid access to lifesaving treatment. I am glad to see the steps the FDA has taken in establishing new post-marketing and surveillance efforts. I look forward to understanding the draft bill that the administration has put forward. There are some new provisions that might enhance the process for both pre-market review and for post-market surveillance. And I look forward to working on this legislation.

I yield the balance of my time.

Mr. PALLONE. Thank you, and recognize the chairman of the full committee, Mr. Dingell.

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

The CHAIRMAN. Mr. Chairman, I thank you for your courtesy. I thank you for holding this important hearing. We are here to discuss the reauthorization of a very important piece of legislation, the Prescription Drug User Fee Act. Originally passed in 1992, this program has provided valuable resources to the Food and Drug Administration to allow timely approval of safe and effective new prescription pharmaceuticals and biologics. Each reauthorization has strengthened the program and we find ourselves with the opportunity to make further enhancements.

I would note that this legislation was the result of discussions between industry, consumers, Members of Congress, and others who were concerned about serious problems in terms of the licensing of new drugs within the FDA's purview. And as a result of the gross inadequacy of funds which existed with regard to Food and Drug and the delay that this was imposing, both on consumers and on industry, the Members of Congress decided that we would work with industry to create a program which would carry out the very important purpose of ensuring that prescription pharmaceuticals came speedily to the market and that there were funds and resources made available to FDA to carry out their responsibilities.

The legislation has worked well. It has been expanded on a number of occasions and it will continue to work better if this committee and the Congress does what needs to be done to see to it that it has continuing sympathetic reauthorization processes which move it forward. I would note that I have seen some, what I regard as, unfair criticisms of the legislation in which it is said that the legislation does not encourage FDA independence in terms of its licensing of new prescription pharmaceuticals.

I know of nothing to support those statements and I would advise anyone who has a different view on these matters to come forward forthwith so that the committee may go into these matters and we may find out whether, in fact, there is something wrong when nothing appears to be wrong. As we consider PDUFA reauthorization, we have to be mindful of two fundamental goals; gaining quicker access to lifesaving products for patients and ensuring that the products that do come to market are safe and effective.

For a cancer patient, access to a lifesaving product in 6 months as opposed to 18 months may be the difference between life and death. Similarly, for that same cancer patient, access to a drug that is neither safe or effective may very well be the difference between life and death. We are going to work to find balance between these concerns. We look to countless Americans who depend on the development of safe, effective and accessible drugs and biologics and speedily so. We recognize the time sensitivity of this reauthorization. The committee must act in a timely manner to prevent possible exit of scientists and other experienced officers at FDA whose positions are funded by user fees.

With this in mind, Chairman Pallone and I have sent a letter to the commissioner of the Food and Drug Administration asking for a date certain by which the agency will begin issuing notices. Coincidentally, the due date of this answer happens to be today. I will expect our witness from FDA to address this issue in her testimony and that we will have the answers to the questions because the continuance of an adequate staff and an adequate mechanism to approve new prescription pharmaceuticals is an urgent matter of concern.

I appreciate the hearing, Mr. Chairman, and the work that user fee stakeholders have put into this proposal. I look forward to the testimony of the witnesses and the input of our members as we discuss the PDUFA reauthorization. Thank you, Mr. Chairman.

Mr. PALLONE. Thank you, Chairman Dingell. I recognize now the gentleman from Indiana, Mr. Buyer.

OPENING STATEMENT OF HON. STEVE BUYER, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF INDIANA

Mr. BUYER. I would like to compliment Mr. Waxman and the Democratic majority, back in 1992, for this legislation. I think, as I look back, also Mr. Dingell and Mr. Waxman, your leadership has made a difference. And so as you look back over the history and all the reauthorizations that we have done, the words that come up are access and safety, but I just want to lay out part of my challenge is the inconsistent use of the language, access and safety.

So as we focus here on PDUFA, I then take a look at other things that we have done. Well, let us see. This Congress just said

let us repeal noninterference, so they want to choose access over the development of new drugs because if you repeal that, I assure you it will have a tremendous impact upon the ability to get new drugs to market. So here the Democratic majority then chooses access over the development of new drugs. Then when it comes to drug re-importation, the Democratic majority will choose access over the safety that is of our closed system.

And then when it comes to the issue on advertising, I am not surprised the Democratic majority would then choose Government regulation or choose censorship over freedom of speech. I don't care, whether I look back, they did that on the V-chip or they will do that now with regard to how we are going to regulate on advertising. I just see inconsistencies. So as I focus here on PDUFA, I am very keen on the language that people use. They will stand up and pound their chest and say we are going to choose safety, we are going to be careful with regard to access; well, at the same time, they want to take our closed system and open it up and say well, it is all about getting drugs from China, anyway, while at the same time are we really protecting people? No. The answer is no, flat out no.

And so I am challenged by, and I am going to be very careful to listen to language that is being used as we go through the reauthorization process here of PDUFA. I just ask that we be consistent so that we can be fair in how we treat people that reside in this country. We should look at this not only from the standpoint of the consumer, the manufacturer, but also, in particular, the Government, as a regulatory function. What information do our scientists, i.e. at FDA, need that is useful so that they can look at these applications? We can increase the quality of the application, reduce the bureaucracies and therefore get that product into the marketplace.

And moving toward this ability to enhance electronic, whether it is filing or the adverse effects, all this will go a long way. And I want to compliment the FDA in putting together this legislation and with that, I will yield back.

Mr. PALLONE. Thank you. I now 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 the hearing on the reauthorization of the Prescription Drug User Fee Act. While this hearing represents the first official step in the health subcommittee's efforts to reauthorize PDUFA, the committee has been working behind the scenes for a long time to take a good look at the relationship between drug manufacturers and the FDA and how that relationship affects the FDA's ability to ensure the safety of our country's drug supply. In the Oversight and Investigation Subcommittee we investigate cases like Vioxx, antidepressants and Ketek and uncovered a bias at the FDA towards swift approval of new drug applications with too little attention paid toward post-market surveillance.

There is no question that PDUFA was initially enacted to ensure drug approval in a more timely manner. In 1992, when Congress first authorized the user fees, patient groups joined the industry in

pushing for this regulatory framework so that those suffering from disease could have faster access to potentially lifesaving drugs. At that time, it took 27 months, on the average, for FDA to review a standard new drug application. That timeframe has shrunk to 10½ months since PDUFA's initial enactment. Unfortunately, the use to be authorized by PDUFA was accompanied by some serious unintended consequences.

As we have learned, over the past few years, its bias toward new drug approval resulted in a culture problem at the FDA where scientists with objections or concerns about the drugs' applications were silenced. We have heard of FDA supervisors telling scientists that their client was the pharmaceutical industry, a statement which flies in the face of the FDA's mission of protecting the public health.

In addition to culture problems, the PDUFA framework has contributed to a structural problem at FDA where the resources weighed heavily in favor of new drug approval. In fact, the Office of Drug Safety receives only one-fourth of the resources and one-seventh of the staff dedicated to the Office of New Drugs. With no independent regulatory authority, the Office of Drug Safety has only few options at its disposal to ensure that drug sponsors make good on their commitment to post-market studies. In fact, the pharmaceutical industry hasn't even begun 71 percent of the post-market studies requested by the FDA, a sign of the industry's lack of regard for the post-market surveillance process in their clear understanding that FDA, can't do much about it.

I think most of my colleagues agree we are going to change that bias during this reauthorization. While I am pleased that the proposal worked out between the industry and the FDA includes a dedicated funding source for drug safety, the $29 million set aside for drug safety represents only 7 percent of the total user fee annually under the proposal. I would like to see more emphasis on drug safety to ensure that the FDA has a workforce level to assure the American people that our drug supply is safe and effective.

Mr. Chairman, I look forward to working with you to accomplish these goals of the PDUFA reauthorization process and I thank our witnesses for appearing today and look forward to their testimony. And with that, Mr. Chairman, I will yield back my time.

Mr. PALLONE. Thank you. Mr. Murphy of Pennsylvania.

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

Mr. MURPHY. Thank you very much, Mr. Chairman. I appreciate you holding this hearing today. I wanted to bring out two parts as we proceed with this to make sure we reviewed these as we look at issues involving drug safety. Not only should we all be concerned about reviewing medications and making sure that medications are brought to the market in a timely manner, but also safely in terms of understanding the impact of their chemical components on persons, as well as their ability to treat disease.

But it is also important, as we review this, that we look at some of the aspects of how medication is prescribed. In particular, the area of psychiatric medications concern me. I previously raised

questions that emphasized that anti-depressant medication should only be prescribed by mental health professionals and accompanied by psychotherapy, particularly with those with depression or bipolar illness. I know, in the past, this committee and other committees have taken up the issue with regard to adolescents, who have increased risk of suicide when they are on anti-depressant medications.

It is important to understand that such medications may change the mood of the patient but do not necessarily change the behavior of the patient and they certainly do not change the cognitive processes of the patient. It is important, I believe, that the FDA works with manufacturers and with prescribers of medication to understand that all of those components are essential parts of dealing with medications in a safe and effective way; not only what they are made of, but how they are used.

I am also hopeful that the final PDUFA language will reauthorize the Best Pharmaceuticals for Children Act to ensure that approved drugs are also tested for practical applications for our Nation's children. We recognize that adult medications tend to move faster than those approved for children and yet, it is important that we not just use adult medications and prescribe them for kids, but really review, in a sound, scientific, reliable and valid way all the aspects of these medications, again, in a way that moves through safely, effectively and efficiently in a timely manner to help our Nation's children.

I appreciate this time and I yield back the balance of it. Thank you.

Mr. PALLONE. Thank you. Gentlewoman from Colorado, Ms. DeGette.

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

Ms. DEGETTE. Thank you, Mr. Chairman. This is a complicated issue to address and I think it deserves careful scrutiny. The goal of PDUFA is to speed up the process by which drug treatments are brought to market in the safest form possible and I think we need to do everything in our power, as we look at reauthorization, to further improve this program to meet that goal. Fifteen years ago PDUFA I was enacted and the original design was simply to provide the FDA with additional funds to reduce a substantial backlog of new drug applications and to speed up the application process to bring drugs to market. Since its inception, PDUFA has evolved to address the ever changing nature of prescription drugs and biologics.

In PDUFA II, Congress required greater transparency in the drug review process, better communication with industry and outside groups and expanded performance goals to activities associated with earlier phases of drug development. PDUFA III further expanded the FDA's role in drug review to include labeling and collecting safety information data, among other things. In spite of PDUFA's evolution into its current incarnation, problems continue to persist in the drug approval process.

Mr. Green and I were just talking about our membership of the Oversight and Investigations subcommittee where we can attest to numerous hearings over the years that there remain a significant number of problems with the drug approval process that have resulted in dismaying health problems for many Americans. Vioxx and Ketek come to mind here. I look forward to listening to the witnesses' testimony today to address the issue of how we use PDUFA to ensure the health and wellbeing of those who take pharmaceuticals and biologics every day.

As we approach the authorization of PDUFA IV, I would like to stress several issues that are important. Because of the problems that have occurred with a number of drugs over recent years, as we have heard, the public has lost confidence in the FDA to protect it from the negative effects of some pharmaceuticals and biologics. The FDA must regain its trust from the American public and show the public that it is truly an independent agency interested only in the public's health. This will mean increased transparency with the drug approval process and more intensive post-market drug review.

Safe and effective drugs are what people expect from the drug approval process and we need to show that such a process exists. As with any situation in which regulators are working closely with entities that are regulated, there are oftentimes people who see that relationship as too cozy. I am interested in hearing from the two panels today about how we might better make clearer distinctions between industry and regulators to further restore the public's confidence.

Mr. Chairman, as with past iterations, this process is an opportunity to improve on the foundation of PDUFA and I look forward to working with you, the committee and those here today to make sure that the health and wellbeing of our country is preserved. Thank you.

Mr. PALLONE. Thank you. The gentleman from Texas, Dr. Burgess.

Mr. BURGESS. Thank you, Mr. Chairman. I am going to submit for the record, in the interest of time. We have got many witnesses who have come quite a distance, far away as northwest Washington, so I will reserve my time for questions.

[The prepared statement of Hon. Michael Burgess follows:]

Mr. PALLONE. Thank you. 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, Chairman Pallone, and thank you to our witnesses for their testimony today at this important hearing. And as we begin our discussion about Prescription Drug User Fee Act and its reauthorization, we undoubtedly will be opening the door to a whole slew of issues related to Food and Drug Administration function. As we discuss each of these issues, we need always to be keeping uppermost in mind the most important issue of all and that is ensuring a safe and affordable drug supply to all Americans within effective timelines. The progress has been made; unfortunately, we have not yet reached this goal.

I understand that my colleagues in other subcommittees and committees have already held hearings on the barriers to ensuring that safe and affordable drug supply that we desire. I hope that today we can build on some of the lessons already learned and the bottom line remains, I believe, two of the barriers are: one: the failure to provide FDA with adequate appropriated funds to fulfill its mission, and second, a system vulnerable to and indeed, plagued by conflicts of interest.

There is something very wrong when the Institutes of Medicine concludes that the drug safety system is impaired. And the General Accounting Office concludes that "FDA lacks a clear and effective process for post-market drug safety issues." Clinical trials are an important component of evaluating drug safety, but they cannot be the only one. We must be more rigorous in monitoring those drugs once they reach the public. Quite frankly, I fear that the failure to properly invest in post-market safety is a result of inappropriate industry influence in the process.

I am also deeply concerned with staffing and structural issues at the FDA that impede optimal results for timely and safe approval of drugs. We simply must do more to attract and retain qualified scientists and then give them the tools to properly monitor drugs continuously through the process of pre-market approval through post-market surveillance. I certainly recognize the impetus for creating PDUFA and for needing additional revenues to get lifesaving drugs out on the market as quickly as it is safely possible.

But unfortunately, we do not have the best possible system in place, even though we are quite aware of what improvements are necessary. As we move through the PDUFA reauthorization process, I hope we can succeed in making the improvements necessary to serve our Nation's public health interests. We have an obligation to do so. 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, and I want to welcome our witnesses who are here. We look forward to hearing from you. Four quick points from me on the issue before us. As we look at the reauthorization, I will say it is nice to see a program that has shown some success and we look forward to hearing about the successes and then also some of the stumbling blocks that may be there.

Second, it is nice to see a program that has a revenue string and then applies it back into its mission. Number 3, that mission of expedited review and safety monitoring, safety of product to the marketplace, Dr. Mullin, I will say it is nice that that is still on the radar, the agency hasn't lost sight of that. And No. 4, I think it is imperative that we realize money does not solve every problem and just giving more money in a budget is not going to take care of any of the obstacles or burdens that are there.

I hope that we will keep our focus on looking at regulation, at duplication, at paperwork, at the burden of bureaucracy that may

be a hindrance—that may be continuing to slow the process and keeping drugs that need to be in the pipeline and to consumers who need to get them. And with that, Mr. Chairman, I thank you and I yield back.

Mr. PALLONE. Thank you. I recognize the gentlewoman from Oregon, Ms. Hooley.

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

Ms. HOOLEY. Thank you, Mr. Chairman. The Prescription Drug User Fee Act has played an important role over the last 15 years in getting drugs and biologics to patients more quickly. Patient access to potential lifesaving drugs was unreasonably delayed before this act was passed. On average, it took over 30 months for a drug to get approved in 1992, before PDUFA. Fortunately, the median time between submission of an application and approval has decreased to less than 14 months as a result of funding provided by PDUFA. However, it is not perfect.

The high proportion of FDA drug review funding provided by user fee is not ideal. Given current budget constraints, user fees are an important and necessary source of funds to get lifesaving drugs to market as quickly and safely as possible. Along with ensuring adequate funding for review of new drugs, it is critical that reauthorization of PDUFA improve post-market safety reviews.

As Dr. Mullin notes in her written testimony, reports of serious and unexpected side effects increased by more than 65 percent in the 3 years between 2002 and 2005. That is an alarming increase and we must ensure that FDA has sufficient resources to analyze adverse events and take action when a pattern of adverse events is recognized.

The FDA recommendation to eliminate the restriction of post-market surveillance to only 3 years after approval is a positive step. There is no good reason why FDA should not review drugs for adverse side effects as long as they are on the market. Larry Kirkwood, a constituent of mine from Molalla, came in to my office last month to share his story about the debilitating stroke he suffered. He believes his injuries were caused by a prescription drug that FDA failed to learn had unexpected side effects until after it was too late for him.

I want to make sure that FDA has sufficient funds to ensure that no one has to wonder, like Larry, whether an adverse health event could have been avoided if they had knowledge of potential side effects learned through more rigorous post-market surveillance. I look forward to discussing the direct-to-consumer advertising provisions recommended by FDA. The FDA is correctly taking an increased oversight role with DTC advertising. However, I want to make sure that the voluntary system envisioned by FDA is sufficient to protect the public health.

Finally, I think it is important to pass PDUFA in a timely manner so that FDA does not lose its best scientists because Congress fails to act before their employees received reduction in force notices. Thank you, Mr. Chairman. I look forward to the hearing.

Mr. PALLONE. Thank you. I recognize the gentleman from Arizona, Mr. Shadegg.

OPENING STATEMENT OF HON. JOHN B. SHADEGG, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF ARIZONA

Mr. SHADEGG. Thank you, Mr. Chairman. I thank you for holding this hearing. The Prescription Drug User Fee Act was originally enacted in 1992 in order to expedite the approval process for drug and biologic applications and drug safety monitoring and I believe we should work together in a bipartisan fashion to reauthorize it. To accomplish its goal, PDUFA requires pharmaceutical companies to pay application fees for each new product, annual manufacturing fees and annual product fees. These user fees have contributed to a 42.5 percent of the FDA's human drug program budget in 2006, roughly $517.5 million.

Prior to the enactment of PDUFA, FDA review for a new drug or biologic averaged 29 months. By 2003, that approval time had dropped to less than 14 months, meaning it had been cut more than in half. The benefit to consumers of speeding up this process is immense in terms of lives saved and health improved. The latest reauthorization, commonly referred to as PDUFA IV, aims to enhance pre-market review of human drug applications, ensure the financial footing of the human drug program and modernize the post-market safety system.

To accomplish these goals, the proposal would increase the overall user fee by $87.4 million above the current levels. I believe these are worthy goals and that it is important for us to steward this legislation through bipartisan passage as quickly as possible.

Mr. Chairman, I look forward to working with you and to hearing from the experts before this committee and to approving reauthorization of a straightforward legislation as quickly as possible and I yield back the balance of my time.

Mr. PALLONE. Thank you. The gentlewoman from California, 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 on reauthorizing PDUFA. I am proud to have worked with former Congressman Jim Greenwood to enact the most recent reauthorization of this legislation and I can't believe how time flies, that we are here again. This is always an important opportunity to not only review what Congress put into place, but the time to review how well it is working. And I think it is one of the most important pieces of legislation that our committee is going to undertake this year.

Prescription drugs and biologics have really changed healthcare as we know it and they continue to improve patient care and to extend lives. Prior to the initial passage of PDUFA, it often took years; not months, but it took years for drugs and biologics to be reviewed by the FDA. They were then strapped for financial and human resources and they were unable to devote enough time and energy to the review process. PDUFA, I think, has come a long way, so that the FDA has the staffing and the expertise to ensure that drugs are safe and reach the patients that really need them.

But there are always tensions in the two undertakings, that it is a timely process so that the most important and the best products move into the marketplace, obviously, to patients, but also that there is the efficacy that the American people have come to not only appreciate, but demand of the FDA. So I think that PDUFA has worked and that it has worked well, but it is not without its problems and the program is not perfect. In fact, I think anything human beings devise is a reflection of our humanity. It is less than perfect.

What I would like to say in this is that I hope, Mr. Chairman, that we will have a clean bill. The whole issue of follow-on biologics or biosimilars is one that is being examined in the Senate and I know that Mr. Waxman is planning to raise here. I do not think that it should be part of PDUFA. There are many complexities to what is being talked about and offered. I think that the committee needs to review that kind of legislation on a stand-alone basis.

I am not so sure what you plan to do with the pediatric legislation. I was Democratic lead on that. I think that that has worked well. I also think that that should be discussed, maybe, in its own hearing, whether you plan to make that part of the reauthorization of PDUFA. I would like to talk to you about it so, I am glad that we are having this hearing. I look forward to hearing from the witnesses. I want to reiterate my support for PDUFA and the user fee program. I think it is a good combination both what the industry does and the funding for FDA and if we need to do more, we need to examine it and make that decision.

Certainly, the American people should have full confidence in FDA and there have been some products that have had to be removed from the market. We need to examine that, why that has happened and I hope that when we come through the other side of this process, that the American people will have even more confidence in the FDA. So thank you for holding this hearing. I look forward to the testimony of those that are going to be here. We have individuals that were a part of our team. Thank you for holding the hearing.

Mr. PALLONE. Thank you. I recognize the gentleman from Oklahoma, Mr. Sullivan.

Mr. SULLIVAN. I waive, Mr. Chairman.

Mr. PALLONE. And the gentleman from Utah, Mr. Matheson.

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

Mr. MATHESON. Thank you, Mr. Chairman. Thank you for holding this hearing. As we will learn today from our panel of experts, new drugs are now available in this country faster than anywhere else in the world. In fact, since its inception in 1992, PDUFA has helped enable FDA to improve more than 1200 new medicines and reduce review times for innovative drugs and biologics, providing patients and doctors with access to breakthrough treatments. And this is an important achievement. It shows that the PDUFA program is meeting its primary goal. I do think we should make every effort to ensure that people have access to effective new medicines as quickly as possible, but with thorough and compliant safety guidelines.

In light of recent adverse drug examples brought before Congress, I look forward to hearing recommendations from our witnesses on how best to achieve the balance between innovation and public safety. As a new member of this committee, I am looking forward to the discussion and recommendations for the reauthorization of this program. And with that, Mr. Chairman, I yield back.

Mr. PALLONE. I recognize Mr. Pitts of Pennsylvania.

Mr. PITTS. I will waive.

Mr. PALLONE. And next is the gentlewoman from Wisconsin, Ms. Baldwin.

Ms. BALDWIN. Thank you, Mr. Chairman. Thank you for holding this hearing and I, too, will waive my opening statement this morning.

Mr. PALLONE. And then we go to Ms. Schakowsky, gentlewoman from Illinois.

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

Ms. SCHAKOWSKY. Thank you. Since its enactment 15 years ago, PDUFA has made a significant difference in the time it takes to get lifesaving prescription drugs into the hands of patients who need them. For many years this has, for many, literally meant the difference between life and death, as the FDA's new drug approval process has been streamlined from 29 months in the 1980s to just 12 months for standard application and 6 months for priority application. This made possible by funding collected by the user fee, which has enabled the FDA to literally double its staff and make major improvements towards technology.

But as I am sure most of us know by now, this user fee is the farthest thing from free money. Coming in at just under 43 percent of the FDA's funding for human drug programs, there is no pretending that the source of this funding plays a small impartial role in policy and procedure at the FDA, far from it. In fact, it is no secret at all that the pharmaceutical industry has been granted a statutory role in directing where the collected user fees will be allocated within the FDA.

Behind closed door with no public input, the industry decides how the FDA will spend this money, speeding up the approval process at the cost, sometimes, of important safety measures. With a fourth PDUFA authorization proposal, including an additional $87.4 million in user fees over the current base, it is well past time for us to start examining what needs to be in place to protect consumers. We need better transparency, better oversight of direct-to-consumer marketing and additional resources allocated to post-market surveillance.

Without these measures, we may only see additional tragedies, like the unacceptable cases of Vioxx and Ketek. The drug industry cannot continue to be given a carte blanche at the FDA. They must be held accountable and we must enable the FDA to increase their authority and transparency throughout their drug approval process. I look forward to what should be a very productive hearing today and I am eager to hear from our witnesses. I yield back. Thank you.

Mr. PALLONE. Thank you. And that concludes the opening statements by members of the subcommittee, so we will now turn to our witness.

I want to welcome Dr. Theresa Mullin. Dr. Mullin is the Assistant Commissioner for Planning with the Food and Drug Administration, and we will now have a 5-minute opening statement from Dr. Mullin. I just want to mention that, in the discretion of the committee, you can submit additional brief and pertinent statements in writing for inclusion in the record. And I will now recognize you for an opening statement. Thank you for being with us today.

STATEMENT OF THERESA MULLIN, ASSISTANT COMMISSIONER FOR PLANNING, FOOD AND DRUG ADMINISTRATION

Ms. MULLIN. Good morning, Mr. Chairman and members of the committee. I am Theresa Mullin, the Assistant Commissioner for Planning at the Food and Drug Administration and I am pleased to be here today to talk about the Prescription Drug User Fee Act, known as PDUFA. As a Director of Planning, I played a lead role in the coordination of implementation of PDUFA III and the ongoing analysis of PDUFA performance and resource requirements. And most recently, I served as the lead FDA negotiator in the discussions with industry related to the reauthorization of PDUFA.

I would like to begin by discussing the successes of PDUFA and FDA's implementation of PDUFA, and also describe some of the challenges that we have tried to address in our recommendations for reauthorization. I will also summarize the highlights of our proposals for PDUFA IV. I would also like to emphasize the importance of a timely reauthorization before the expiration of this program in September of this year.

Let me start by saying that FDA considers the review of safety and effectiveness of new drugs to be a central part of its mission of protecting and promoting public health. As you know, Congress enacted PDUFA in 1992 and its been reauthorized twice since then. The law provided added funds that made it possible for us to hire additional reviewers and update our IT systems to support drug review. At the same time, we committed to providing a complete review in a faster and more predictable timeframe. But prior to that, our drug review process was understaffed and slow and it delayed access to new medicines for patients in the United States.

PDUFA enabled us to increase the speed of the application review without changing our standards for safety and effectiveness. And this has also led to a shorter time to marketing approval for those drug applications that have met the standards. The median time for approval for priority drugs and biologics has been reduced from a median of 15 months in 1993 to a median of 6 months in 2006. And a priority designation means that it is a new drug that offers a significant advance over existing treatments. Earlier access to new drugs has provided important benefits for patients.

Since the enactment of PDUFA, FDA has approved over 1,200 new drugs and among those approvals, 76 new drugs for cancer, 178 new anti-infective drugs, 111 new drugs for metabolic and endocrine disorders, 115 new drugs for neurological and psychiatric

disorders, 80 new drugs for cardiovascular and renal disease, among many other new medicines.

PDUFA has been successful in speeding access to new drugs, but the program has also faced challenges and I would like to talk briefly about the challenges. First, program costs, including payroll and rent related cost, have really outpaced the funding. And second, the review workload has grown significantly, particularly review activities that are not accounted for in the current workload adjustor. There has been an increasingly dramatic growth in the number of consultation meetings requested by companies during the drug development phase.

For example, in the year 2000 meetings scheduled at the request of drug sponsors grew by 72 percent and now we are up to, last year, 2,288 meetings requested by companies for consultations. That translates into more than nine industry meetings per business day. And the same people who are doing those meetings are doing drug reviews and all the other work. These meetings are very useful. They basically help to improve the drug development program and it is a benefit to the patients who are then going to be participating in the clinical trials in that program. But they are also very labor intensive.

The third challenge is the growth in the volume of post-market safety work and our system hasn't kept up. For example, the number of serious and unexpected adverse events grew by over 65 percent between 2002 and 2005. We need the capacity to review and respond in a timely manner. PDUFA currently allows for fee supported post-market activities, but it is only for up to the first 3 years after approval and only for those products approved after October 1 2002. Our analysis of the timing of safety related labeling changes has found that the majority of those changes occur after the first 3 years that a product is on the market.

In our most recent reauthorization, PDUFA III, Congress directed FDA to consult key stakeholders in developing our reauthorization recommendations. We began with the public process in November 2005. We had a public meeting on PDUFA and asked stakeholders to tell us what they thought should be changed and what should be retained in the program the following year. In 2006, we had meetings with the patient groups, consumer groups and health professionals to, again, follow up and find out what they thought we ought to be doing to improve the program.

Now, in these meetings, some stakeholders felt concern that we rely on user fees at all, but most felt that we really needed to have strong support to keep the review program strong and adequately staffed. Nearly all expressed the view that we ought to be spending more on post-market safety in PDUFA and many thought we should be expanding our capacity for the review of direct-to-consumer advertising. In our discussions with industry and in development of recommendations, we have tried to address those concerns, as well as our own.

I would now like to highlight the four key recommendations that we have for PDUFA IV. The first is to put the new drug review program on a sound financial footing. User fees have provided substantial resources to FDA, but they haven't kept up with the increasing cost of the program due to inflation and this expanding re-

view work load. And so we are proposing changes to the financial provisions of PDUFA that would correct for these shortcomings.

Second, we are recommending enhancements in two areas of pre-market review; first, to expand our work in the good review management principles for efficient and effective pre-market review and second, to conduct some initiatives so that we can enhance the science base and upgrade the science base of our review process and also develop guidance to improve and expedite critical drug development.

And third, we are recommending changes to modernize the post-market safety system. We are recommending increased funds and the removal of the date limitations on the use of those funds for post-market safety and we are recommending increased funds to first conduct studies to be sure we are applying the most effective tools for collection of adverse events. We also want to expand our access to better patient population databases for epidemiology.

Training for the post-market safety area, our standards for epidemiology studies, evaluating what really works in risk management post-market. And finally, direct-to-consumer advertising. We are proposing a separate user fee for direct-to-consumer advertising because stakeholders expressed concerns about this and we are proposing a separate program for that and so that we can conduct a more timely review of the ads submitted to us for comment, for advisory review so we can weigh in on whether those ads are accurate and adequately balanced and adequately supported. My final point is just, and I have heard it many times, about the need for reauthorization and that we want to work with you in whatever way we can to support that. Thank you. I will be happy to answer any questions.

[The prepared statement of Ms. Mullin follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

STATEMENT BY

THERESA M. MULLIN, PH.D.
ASSISTANT COMMISSIONER FOR PLANNING
FOOD AND DRUG ADMINISTRATION

BEFORE THE

SUBCOMMITTEE ON HEALTH

COMMITTEE ON ENERGY AND COMMERCE

UNITED STATES HOUSE OF REPRESENTATIVES

April 17, 2007

RELEASE ONLY UPON DELIVERY

INTRODUCTION

Mr. Chairman and Members of the Committee, I am Theresa Mullin, Assistant Commissioner for Planning at the Food and Drug Administration (FDA or the Agency).

I am pleased to be here today, to talk about the Prescription Drug User Fee Act, or PDUFA. As the FDA Director of Planning, I've played a lead role in coordinating implementation of PDUFA III initiatives, and the on-going analysis of PDUFA performance and resource requirements. Most recently, I served as FDA's lead in the discussions with industry related to the reauthorization of PDUFA.

I'd like to begin by discussing FDA's success in implementing PDUFA and describe some challenges that we have tried to address in our recommendations for reauthorization. I will also summarize highlights of our proposal for PDUFA IV.

Before proceeding, however, I would like to emphasize the importance of timely reauthorization of this law. The Agency and the staff charged with implementing PDUFA III need to be confident that reauthorization will occur by the end of September.

BACKGROUND

FDA considers careful and timely review of the safety and effectiveness of new drug applications (NDAs) and biologics license applications (BLAs) to be a central part of FDA's mission to protect and promote the public health.

Before PDUFA, FDA's drug review process was not very predictable, and it was relatively slow. At the same time, regulators in other countries were able to review products faster. Access to new medicines for U.S. patients lagged behind. In 1992 Congress enacted

PDUFA, which provided the added funds through user fees that enabled FDA to hire additional reviewers and support staff and upgrade its information technology systems. At the same time, FDA committed to complete reviews in a predictable timeframe. These changes enabled FDA to speed the application review process for new drugs and biologics without compromising FDA's high standards for approval. PDUFA has since been reauthorized twice. In the most recent reauthorization, Congress directed FDA to consult with key stakeholders in developing recommendations for PDUFA reauthorization. This includes the House Committee on Energy and Commerce and the Senate Committee on Health, Education, Labor, and Pensions, as well as appropriate scientific and academic experts, health care professionals, patient representatives, consumer advocacy groups, and the regulated industry. We have complied with these requirements in preparing our PDUFA IV proposal.

PDUFA ACHIEVEMENTS

PDUFA has produced significant benefits for public health, including providing the public faster access to over 1200 new drugs and biologics since enactment in 1992. During the PDUFA era, FDA has approved many hundreds of important new medicines including treatments for cancer, infectious disease, neurological and psychiatric disorders, and cardiovascular diseases.

PDUFA implementation efforts have reduced product review times and eliminated the earlier lag in availability of new drugs to U.S. patients. The median approval time for priority drug and biologics applications has been reduced from 14 months in fiscal year (FY) 1993 to a median of six months in FY 2006. Priority applications are those for new drugs offering a

significant advance over existing treatments. Applications for drugs similar to those already marketed are designated "standard". For standard NDAs, the median approval time was 22 months in FY 1993. By FY 2006, the median approval time had declined to 16 months for standard NDAs.

Along with these successes, the drug review program also has faced challenges. Program costs, including payroll and rent-related costs, and review workload continue to grow as more companies seek FDA advice during drug development, requesting meetings and special protocols assessments from FDA. This increased workload has not been reflected in the current fee adjustments.

The volume of post-market safety reports also has grown and has put a strain on our post-market capacity. For example, the number of reports of serious and unexpected adverse events has jumped by more than 65 percent in 3 years, from 129,000 reports in 2002, to 214,000 in 2005. PDUFA currently allows for fee-supported post-market activities, but that support is restricted to the first three years after marketing approval and it applies only to drugs approved after October 1, 2002. A recent analysis of safety-related labeling changes has found that the majority of those changes occur after the product has been on the market for three years.

FDA RECOMMENDATIONS FOR PDUFA IV

We have developed our recommendations in a manner designed to solicit broad and repeated public input. We began to seek public comment on PDUFA reauthorization at a public meeting in November 2005. We also had follow-up meetings with patient groups, consumer groups and healthcare professionals during 2006. Some participants expressed concern about

reliance on user fees. Almost all expressed support for more FDA resources to keep the review process strong and adequately staffed. And virtually all expressed the view that PDUFA should provide increased funding for post-market safety. Many of the public stakeholders who talked to us also expressed the view that FDA should expand its capacity to review direct-to-consumer (DTC) advertisements.

During 2006, we also held discussions with representatives from the pharmaceutical and biotechnology industries. In those discussions, we raised the concerns we heard in our meetings with other stakeholders, as well as our own concerns. The proposed changes we are recommending respond to many of those concerns and address FDA's goals for PDUFA IV.

1. ENSURE SOUND FINANCIAL FOOTING

Our first recommendation is to put the new drug review program on a sound financial footing. User fees have provided substantial resources to FDA, but these resources have not kept up with the increasing costs of the program due to inflation and the expanding review workload. The PDUFA III provisions for annually adjusting fees for inflation and workload have not adequately accounted for actual growth in costs and workload. Therefore, we are proposing changes to the PDUFA financial provisions to correct for these shortcomings.

In terms of payroll costs, PDUFA currently allows for adjustments for federal pay increases, but not full payroll cost increases, which would include the cost of employee health benefits, retirement benefits and other payroll compensation costs. While federal pay increases have grown at an average of 4.2 percent over the past 5 years, total payroll costs for FDA have grown at an average annual rate of 5.8 percent. In PDUFA IV we recommend changing the calculation of inflation adjustment to include the actual FDA rate of increase in total payroll

costs –including salary and benefits per full-time equivalent (FTE)--over the most recent 5-year period.

Rent and rent-related costs have also been increasing. Between fiscal year 2001 and 2005 rent and rent-related costs have gone up over 21 percent per FTE and these cost are expected to increase as we continue to move to the White Oak facility. Part of this cost reflects the increased building security requirements during recent years. We did not account for this cost growth in our current annual fee adjustments.

In addition, fee adjustments for workload should more accurately reflect the full scope of FDA review activities. For example, since FY 2000, meetings scheduled at the request of drug sponsors grew by 72 percent, up to 2,288 meetings in FY 2006. This figure translates to more than nine formal meetings per business day. But the current workload adjuster does not account for this dramatic increase. We recommend that the PDUFA IV workload adjuster be refined to include adjustments for growth in the number of meetings and special protocol assessments for investigational new drugs, and growth in the volume of labeling supplements and annual reports submitted for FDA review.

To pay for these proposals for sound financial footing, as well as for enhancements to pre-market and post-market review, that will be discussed shortly, we are recommending that PDUFA fees be increased by $87.4 million per year. This increase yields a total of $392.8 million in user fees in FY 2008. However, I note that this total is calculated based on the PDUFA workload through June of 2006. We expect that the final total would be higher once we have the workload data through June of 2007. We've estimated that with that 2007 data, the total fee funding during the first year of PDUFA IV would be on the order of $437.8

million. This amount would be adjusted in later years based on measured changes in inflation and workload.

The recommended increase of $87.4 million would include $17.7 million to pay for salary and benefit increases; $11.7 million to pay increased rents and rent-related costs like security, and a share of the costs of FDA's move to the new White Oak facility in Silver Spring, Md. The proposed increase also includes $20 million to cover significant increases in the drug review workload that were incurred but not compensated for under PDUFA III. These costs could be supported under PDUFA IV, and these costs are expected to continue.

The recommended increase of $87.4 million also includes $37.9 million in enhancements to the drug review program. These would be in two basic areas: First, proposed enhancements to the pre-market review process. Second, proposed modernization of the post-market safety system. I'll next describe proposed enhancements to the drug review program, covering these two basic areas. Then I will turn to a proposed new program to assess user fees for advisory reviews of DTC television ads.

2. ENHANCE PROCESS FOR PRE-MARKET REVIEW

For PDUFA IV, FDA recommends enhancements in two areas for the pre-market review process: 1) expanding the implementation of Good Review Management Practices (GRMPs) developed under PDUFA III and 2) undertaking some additional initiatives designed to help expedite drug development. In the area of GRMPs, we propose to further implement the principles and goals for enhancing the efficiency and effectiveness of our review process that were outlined in our 2005 guidance document, *Guidance for Review Staff and Industry on Good Review Management Principles and Practices for Prescription Drug User Fee Act*

Products. We would expand the implementation of GRMPs by developing a planned timeline for the review of the application with particular attention to elements such as 1) discussion of labeling and post-marketing study commitments; 2) decision-making; and 3) documentation of such decisions in the administrative record by the signatory authority. By providing such a timeline, applicants will better understand FDA's review plan and when to expect feedback from the Agency on important issues such as application deficiencies, labeling, and post-marketing study commitments.

The PDUFA IV proposal also includes an increase of $4.6 million in user fees to fund additional staff to further enhance the science base of our review processes and to develop guidance documents to assist in clinical drug development, including several guidances related to clinical trial design. Clarifying FDA's expectations on important topics such as clinical trial design will enable the industry to focus their efforts on useful trials and decrease less useful experimentation. Increased resources also would free up reviewer time for greater participation in scientific training and research collaborations that will ultimately help clarify regulatory pathways for development of promising future therapies.

Lastly, the PDUFA IV proposal includes a $4 million increase in funding to further improve the information technology (IT) infrastructure for human drug review, to move FDA toward an all-electronic drug review system.

3. MODERNIZE AND TRANSFORM THE POST-MARKET DRUG SAFETY SYSTEM

FDA would also use the proposed PDUFA IV funds to 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 would include $29.3 million and hiring 82 additional staff for post-market safety activities. This would triple the amount of user fee funding available to improve the post-market drug safety system. We also propose to eliminate the current statutory time limit that restricts user fee funding of 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 limitation will provide enhanced funding for the assessments of drug products over time, to adequately manage drug risks, regardless of a drug's approval date. Among other initiatives described below, FDA would use the increased funds to further enhance and improve communication and coordination between FDA pre-market and post-market review staff, a key recommendation made by the Institute of Medicine in their September 2006 Report.

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 procure external 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. Such studies would attempt to answer central questions related to: 1) the number and types of safety concerns that are discovered by various types of adverse event collection; 2) the age of the medical products at the time such safety concerns are detected; and 3) the types of actions that are subsequently taken and their ultimate effect on patient safety.

The proposed funds also would be used by FDA 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 obtaining access to additional drug safety information beyond that discovered through spontaneous adverse event reports, including population-based epidemiological data and other types of observational data resources. In addition, fees would support additional training for our current staff, and hiring additional epidemiologists, safety evaluators, and programmers who can best use the existing and new adverse event information.

PDUFA IV also would allow us to develop a plan to evaluate current risk management plans and tools. We would hold a public workshop to obtain input from academia, industry and other stakeholders regarding the prioritization of the plans and tools to be evaluated. The evaluation would include assessments of the effectiveness of identified Risk Minimization Action Plans (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.

We would also 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 a safety workflow tracking system, to support access to and analyses of externally linked databases, and to enhance FDA's AERS and surveillance tools.

4. REVIEW OF DIRECT-TO-CONSUMER (DTC) ADVERTISING

We also are proposing a new program to assess fees for advisory reviews of DTC television advertisements. Research has shown benefits associated with DTC prescription drug television advertising, such as informing patients about the availability of new treatment options and encouraging patients to see a physician about an undiagnosed illness. However, some have expressed concerns that DTC advertisements may overstate benefits or fail to fairly convey risks.

Currently, companies have the option of submitting their planned advertisements to FDA for advisory review before public dissemination. This approach provides the benefit of FDA input on whether or not the advertisements are accurate, balanced, and adequately supported, enabling advertisements to be changed, if necessary, before they are shown to the public.

Companies recognize the benefits this advisory review mechanism offers. However, though FDA's DTC advisory review workload has been steadily increasing, our staffing for this activity has remained relatively level.

Therefore, we propose creating a separate program to assess, collect, and use fees for the advisory review of prescription drug television advertisements. These user fees would not be funded by application, product, or establishment fees assessed under PDUFA. Instead, these

new fees would be assessed separately and collected only from those companies that intend to seek FDA advisory reviews of DTC television advertisements. This program would provide for increased FDA resources to allow for the timely review of DTC television advertisement advisory submissions and ensure FDA input on whether or not the advertisements are accurate, balanced, and adequately supported.

To ensure stable funding for the program in case the number of advisory submissions fluctuates widely from year to year, the program would assess a one-time participation fee to be placed in an operating reserve. The program would then charge fees each year for each advisory review requested. These new fees would provide sufficient resources for FDA to hire additional staff to review DTC television advertising submissions in a predictable, timely manner. FDA anticipates collecting $6.25 million in annual fees during the first year of the program (and a similar amount to go into an operating reserve fund) to support 27 additional staff to review DTC television advertising. Advisory review fee amounts would be adjusted annually for inflation and to take into account increases in workload. As part of this program, FDA is proposing to commit to certain performance goals including review of a certain number of original advisory review submissions in 45 days and resubmissions in 30 days. The goals would be phased in over the 5 years of the program to allow for the recruitment and training of staff.

CONCLUSION

PDUFA III expires on September 30, 2007 and I want to re-emphasize the importance of achieving a timely reauthorization of this law. FDA is ready to work with you to accomplish this goal. If we are to sustain our record of accomplishment under PDUFA III, it is critical

that the reauthorization occur seamlessly without any gap between the expiration of the old law and the enactment of PDUFA IV. Any delay in the reauthorization of this program could trigger erosion in our work force, particularly among senior reviewers whose skills are in very high demand. The repercussions of such a loss would be with us for years to come.

Thank you for your commitment to the continued success of PDUFA and to the mission of FDA. I am happy to answer questions you may have.

Mr. PALLONE. Thank you. Thank you very much and now we will take some questions and I will recognize myself for 5 minutes for that purpose.

My first question relates to what Chairman Dingell said and you mentioned, the need for timely reauthorization. A few weeks ago, Chairman Dingell and I wrote to Dr. von Eschenbach asking for a day certain as to when he would be forced to send a reduction in force or RIF notice to FDA employees should the user fee program fail to be authorized before September 30. Under part 351 of title 5, Code of Federal Regulations, the commissioner would have at least 60 days to issue a RIF notice and that would put us at the end of July that we would have PDUFA reauthorized or on its way to the White House.

We are asking this so as to understand the timeframe, we can ensure that there is no personnel disruptions with the program, so my questions really are first, do you have that date for us with regard to the RIFs and second, would there be any reason to move the date up to the end of June or sooner? This is all for the purpose of getting this done in a timely fashion, obviously.

Ms. MULLIN. Well, as you said, the regulations require that we give individual employees 60 days notice. Substantial planning has to go into identifying the employees and putting that RIF into effect. The union would also need to be notified of it and it is a fairly complex process. We would like to submit the longer description of what has to be done in order to carry out that process, but I guess the larger point for us, as you say, is that when employees become aware that a process is underway, we are concerned that they may begin to look for something else to do.

Mr. PALLONE. But are you going to give me a date because Mr. Dingell insists on regular order around here and we want to be orderly.

Ms. MULLIN. I wish I could give you a specific date. I do have one and I would like to go back and have the longer description of what has to be done provided to you. I do know that reauthorization in June or at least mid-July would be most preferred, I would say.

Mr. PALLONE. OK. Well, that is helpful. Thank you. Second question. The PDUFA IV proposal is a result of a compromise between FDA and stakeholder groups. What are some of the items that were included in the initial discussions that were left out of the final proposal?

Ms. MULLIN. Well, in terms of the safety package that we have, we essentially have gone into the package, it is all of our priorities FDA identified for drug safety and the entire package was supported. FDA, in its own, looking at other programs, for example, in the DTC area, has focused on TV advertisement as a place where we can really sort of have a great impact, we think, and we actually have the data to actually structure and go in there and start a program data on the workload that is there today so we can estimate what it would take. I would have to say that in terms of resourcing for what we wanted to get that we really did come out of it with the things that we went in and wanted to have.

Mr. PALLONE. So you don't think there are any items that were in the initial discussions that were left out, for the most part?

Ms. MULLIN. No, I don't think we really got the things that we were hoping to get.

Mr. PALLONE. OK. Now, you mentioned, in your written testimony, that the number of reports of serious and unexpected adverse events has jumped by more than 65 percent in 3 years. In your opinion, is there a correlation between those reports and the fact that user fees are becoming a larger and larger portion of the FDA budget?

Ms. MULLIN. In my opinion, there is no relationship between those two things.

Mr. PALLONE. OK. And then I wanted to ask you, finally, according to the data analyzed by Harvard professor, Daniel Carpenter, drugs approved just before PDUFA deadlines are far more likely than those approved at other points in the review cycle to cause safety problems after they are in widespread use. Do you agree with that assessment?

Ms. MULLIN. I had heard about that finding. I haven't read his paper and I really don't feel I can comment on it. I just really don't think I can make a comment on it.

Mr. PALLONE. What I am trying to get out is whether there is any indication that PDUFA timeliness and PDUFA timelines compromise the safety of new drugs and biologics. If you don't think that is true, do you have——

Ms. MULLIN. Well, we don't believe that there is a problem. We don't think that the timelines have any effect on the safety or the issues that he points out by, like I said, I don't really know what is in his paper, but that has not been our experience. We don't think there is a relationship there.

Mr. PALLONE. Do you have any evidence you could submit to us in writing that would contradict what the professor is saying?

Ms. MULLIN. I think we would be happy to provide a more thoughtful and to go back and look at that paper response to that for the record.

Mr. PALLONE. I would appreciate it. Thank you. Mr. Deal.

Mr. DEAL. Thank you. I would like to ask you if you could elaborate on the whole issue of health information technology. Let me couch it in two particulars. Last year, as we were trying to pass an expanded health information technology bill, one of the things we were trying to promote was non-identifiable health information that could assist in a variety of areas; further development in research, et cetera. And I guess my concern is what is the current situation with regard to your ability for data mining through health information technology to determine adverse events and to what extent could that be expanded and to what extent would the funding that is in this proposed legislation assist in that regard?

Ms. MULLIN. Our current post-market safety system relies primarily on a passive reporting approach and we receive information through passive surveillance. I believe what you are describing is moving more toward what is called an active surveillance system and the proposals that we have for post-market safety in PDUFA IV would move us and position us to be ready to begin, but be ready to be a part of that kind of system which is often described and I think, envisioned as a consortium or partnership with many,

many parties participating is how I think the department has conceived it, as well.

We have talked about a sentinel system, for example. But to do that, we need to have the infrastructure that can allow us to link, have access to linked databases, these kinds of population databases that we are talking about and so we need to have that. We would need to have better tools, analytic tools, for mining appropriately using those kinds of data and as I mentioned, in our packages, best epidemiology practices so the people's methods for looking at these very complex data sets are consistent to well-understood, so people aren't arguing about the findings because they don't agree on the methods. So we want a process where we involve academics and industry and other members of the public in trying to identify and discuss that so we can identify best practices for using those kinds of data sets, as well. And we have put in some resources for moving toward that kind of approach in PDUFA IV.

Mr. DEAL. I think one of the things that we all have concerns about is that we have some overall and overarching policy considerations as we deal with a variety of issues, and I think the information technology gathering process is very important, especially as we deal with things like follow-on biologics and the pharmaceuticals associated with all of that entire area.

I know this is not exactly within the scope of what you are here to testify about today, but I would hope that FDA would provide this committee with your points of view as it would regard how we would structure this non-identifiable information that would be most beneficial to you. For example, I know that in the projects that are ongoing now with reporting of information by physicians and others and moving toward perhaps they pay for performance arrangement. I would hope that we would have the information that is being gathered there in a format that would be compatible with FDA utilizing that information.

Sometimes I think we do things in little categories of their own and do not have concern for how they could interact with and impact on other areas of what the Government is doing in different agencies. So I don't think it necessarily requires a response from you here, but I would hope that as we move forward looking at these areas such as health IT, that FDA could give us some insight as to what, if anything, we could do that would facilitate your activities, particularly as it relates to the post-approval adverse event categories. Thank you, Mr. Chairman.

Mr. PALLONE. Did you want to respond?

Ms. MULLIN. My comment there would be that the department is undertaking an effort to look at, certainly under the AHIC, as it is called, under Secretary Leavitt and the Office of National Coordinator, are focusing on interoperability standards to be sure that we do have the kind of capabilities you are describing and FDA is fully participating in that process.

Mr. PALLONE. Thank you. Mr. Waxman.

Mr. WAXMAN. Thank you, Mr. Chairman. Dr. Mullin, thank you for your testimony. The industry/FDA proposal would expand the use of the user fees to some important post-market safety activities and this is a positive development. I want to ask you more about this. The proposal specifies that FDA may apply user fees to things

like (1) collecting and reviewing post-market safety information; (2) developing improved adverse event data collection systems; and (3) expanding FDA's analytical tools to assess potential safety problems, including access to external databases.

And yet, under the proposal, only $29 million would be devoted to these activities; the remaining $360 million would continue to be spent on review activities. In its report, the IOM set forth some rough estimates for how much funding it would take to conduct enhanced drug safety activities, including many activities described in the industry/FDA proposal, they came up with something more in the range of a $100 million to $200 million. So I am deeply concerned that $29 million is just not going to be enough. At the outset of the FDA and negotiation with industry, how much did FDA request for drug safety activities?

Ms. MULLIN. At the outset of our discussions, we, as I mentioned a minute ago, wanted the set of items that we proposed and we have a base amount of spending already in the post-market area, although it has the time restrictions on it, and it is on the order of about $15 million a year that we currently have from user fees that we spend on post-market safety, as opposed to the broader drug safety, of course, which a great deal of which happens in premarket. But $15 million, 30, 29.3 is added to that and this is again focused on these post-market activities. But we focused on the set of things that are post-market safety.

Mr. WAXMAN. You thought this amount of money is sufficient? You didn't ask for more.

Ms. MULLIN. We thought it was sufficient to cover the things that we thought were our highest priority. It would certainly not cover everything that is recommended in the IOM report.

Mr. WAXMAN. Let me ask you this. If all you asked for was an additional $29 million, would this create an optimal drug safety system? If not, what else is needed?

Ms. MULLIN. I think it doesn't create the system mentioned in the IOM report, which is a much more expansive effort, but it gives us a very strong safety system that we think is a significant improvement and will provide a very strong capability for us.

Mr. WAXMAN. One of the recommendations that the IOM made was to do something about FDA's lack of authority to require drug manufacturers to take certain critical actions with respect to drug safety. For example, FDA is unable to require manufacturers to conduct post-market studies. Under the current law, FDA could ask a manufacturer to conduct the studies and then hope that they are actually done when the manufacturer has agreed to FDA's request, but if later they don't do the studies—and most of them appear not to—FDA's only option is to remove the drug from the market, something that FDA has never done and isn't likely to do, given the significant patient populations that come to rely on these drugs.

I know that one of the performance goals contained in the industry/FDA PDUFA proposal is develop standard operating procedures that would clarify FDA's policies and procedures with respect to requesting voluntary study commitments, but this obviously does nothing to address the very critical fact that FDA is entirely unable

to require that these studies be done in the first place or that they be completed. This is not, of course, just a theoretical problem.

According to FDA's own data in 2006, there were 1200 open or ongoing commitments to conduct post-marketing studies, but manufacturers ended up completing only 11 percent of these studies that year; 71 percent of these studies hadn't even started. Do you think this is acceptable? Do you agree the PDUFA package does nothing to change the fact that FDA lacks the authority to require post-market studies because FDA would need Congress to act to address that problem?

Ms. MULLIN. Well, I will go back and begin with the IOM report and I know those recommendations were in there. The IOM report had recommendations——

Mr. WAXMAN. Well, I am not talking about the report. I am asking specifically on this issue, on this recommendation that you be able to require these studies to be done.

Ms. MULLIN. I will begin, if I may, just saying that the recommendations that they made were for FDA, some recommendations for the department and some for Congress and regulatory authority recommendations were directed at Congress and my role in doing these PDUFA discussions has been to focus on getting better resourcing for the current authority and so we can do a better job——

Mr. WAXMAN. Well, don't you think in addition you ought to have that authority to require the manufacturers do the study?

Ms. MULLIN. I can't really speak to that, but I can say that what we have in the PDUFA that we are recommending is additional resources so that——

Mr. WAXMAN. Well, I know you are satisfied with what you have, but don't you think you ought to have more, given your experiences at FDA in this area?

Ms. MULLIN. I am really not an expert on that and I can't really speak to that.

Mr. WAXMAN. Thank you. Thank you, Mr. Chairman.

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

Mr. BUYER. I would like to follow up where, on Mr. Waxman's, but take a different course on the post-market review. I noticed, over the years, the FDA has been very concerned with regard to the number of counterfeit drugs that are coming into our country. So here we can focus on the perfection of a closed system, while at the same time we have cracks in that closed system. So the Internet has exploited this and so we have many of our citizens think that they are getting drugs from Canadian pharmacies when, in fact, the FDA, in cooperation with United States Customs and Border Protection, you have been conducting surveillance.

So whether it has been in 2001, 2003, 2004, 2005, you have been going to different ports of entry, examining parcels that come in to the hubs and you have been determining that many, each one, there are different percentages; 60, 70, 80, now it is 90 percent of the drugs that they examine are non-FDA approved drugs. So if we are going to look at this post-market review and how you are able to come up or perfect a particular system, I look at this and say my gosh, if we have got so many unapproved FDA drugs, obviously,

there would be then a lack of assurance with regard to safety, effectiveness, quality and purity.

And if the FDA cannot assure the safety and efficacy of a drug product line that is coming through these types of sources, because you have not been able to review or you didn't review or approve, nor have you had accessibility to monitor the manufacturing and quality control of a particular facility from a particular country. And if they are coming from 27 different countries through these types of sources, I don't know how you can sit here before us and say well, we are going to have a wonderful monitoring system here.

We go to page 8 of your testimony. On page 8 of your written testimony in discussing the post-market review of drugs, it says the FDA intends to use additional resources "to improve our tools for detection of adverse events." My question, now, is knowing that we have this exploitation that is occurring from other countries to gain access to our system and there are people even sitting here in this panel before you that think that will this get access to people? To heck with safety. Let us go with a populist issue. So to what extent has the FDA factored in counterfeit drugs and what effects will FDA pursue to combat counterfeit drugs in this post-market review?

Ms. MULLIN. The post-market compliance issues that you refer to are currently outside the scope of what is defined as human drug review in the statute and our recommendations for PDUFA IV would still not include post-market compliance issues in the area that you are talking about.

Mr. BUYER. Time out for just a second. We are going to reauthorize this. If I had a particular drug that is on the market and if, oh, take a step back. A manufacturer puts a drug on the market and the doctor has prescribed this particular drug to the patient. The patient begins to take that drug and then thinks that well, I can get that drug cheaper, so I will get it through a Canadian source and what we have happening is, is that there are adverse effects that don't even end up being reported. So my question to you is how can we have an effective system if we have this prevalency occurring with regard to the number of unapproved FDA drugs and many, many drugs that are coming onto the marketplace? How can we improve this detection system?

Ms. MULLIN. Well, some of the adverse event reports we may be getting now may be the result of the use of counterfeit medications and we are going to continue to monitor adverse events and try to understand the context of the care in which they occurred so we can identify what the source of harm was.

Mr. BUYER. Do we know that of the 60 percent increase of adverse effects over the last 3 years, do we know the impact of the counterfeit drugs are having upon that number?

Ms. MULLIN. I don't think we do, but I have to say we are really outside of the scope of my expertise and if you would like, we can certainly go back and talk to the experts who focus on the counterfeit drug issues at FDA and provide you an answer for the record.

Mr. BUYER. I just don't know how we can have, how we can best protect the American people and give them the assurances of a drug's safety if we are going to permit this exploitation and damage to our drug supply and then in turn, beat up the manufacturer. I

would like to work with you on figuring out how we can expand the scope and go after these counterfeiters. I yield back.

Mr. PALLONE. Thank you. The gentleman from Texas, Mr. Green, our vice chair.

Mr. GREEN. Thank you, Mr. Chairman. Again, welcome, Dr. Mullin. Former FDA Commissioner Mark McClellan has advocated for a more robust system to monitor post-market risk. In testimony delivered to the Senate Health Committee and in a recent New England Journal of Medicine article, he writes the problems in the current adverse events reporting system are spontaneous and by design, can only capture a small fraction of the problem. To improve surveillance, Dr. McClellan proposes that risk information be gathered through an electronic and active surveillance system network.

We know that data exists already through private health insurers and within the Medicare and Medicaid programs. In fact, I know at least one pharmacy benefit manager that thanks to its electronic data, knew about the Vioxx problem and pulled Vioxx before even the FDA took action. Can you comment on Dr. McClellan's proposal to what additional funds would be needed to implement it and how it could complement existing surveillance systems at the FDA to catch these problems sooner?

Ms. MULLIN. Well, we think that the active surveillance approach that Dr. McClellan is describing is really the way of the future. We think that is the way we want to go in the future. I think that what we have in our package of proposals for PDUFA IV, as I am saying, it really helps us to move and be positioned to be able to work effectively with that kind of pooled population data. The scope of such a system that is envisioned is not there yet today. Those electronic health records are definitely beginning to become available, so we are moving in that direction.

What we are doing, to be ready for that kind of system which I have often heard described as perhaps something where there will be multiple parties involved, shared resources and so forth, in the future where we want to be ready for that, to be participating in it and so the tools and moving the infrastructure, our IT infrastructure, that way is critical for our being ready to be participants in that, as well.

Mr. GREEN. So whatever we reauthorize under PDUFA, we need to make sure the resources are there so the FDA can do their job with that——

Ms. MULLIN. I think FDA would want to participate and want to be involved in that.

Mr. GREEN. OK. I would like to explore the new user fee for the direct-to-consumer advertising. As you mentioned in your statement, companies currently have the option of submitting ads before public hearing. To your knowledge, what percentage of drug advertisements are submitted to FDA for pre-screening?

Ms. MULLIN. Our data suggests that about a third of those direct-to-consumer advertisements that are broadcast on TV are currently submitted for pre-review.

Mr. GREEN. OK. I understand that the new user fee would be sufficient to hire 27 additional staff to review the ads. Is it true

that the review would still be voluntary for industry in the proposal?

Ms. MULLIN. Yes. Under our proposal, which is the current authority, it would be a voluntary review.

Mr. GREEN. What element of the proposal, if any, would provide additional incentives to submit their ads?

Ms. MULLIN. We think that companies would—well, first of all, we arrived at this proposal and I think it received the support and endorsement of the industry, including, I would assume, the companies that would be participating in such a program. But we think the incentives would be that if you are going to put out a new ad and spend a great deal of money on broadcast, TV broadcast ads, that it would be certainly advantageous to participate in this and get FDA's views before you run the ad about whether or not we consider it to be compliant rather than having to say have it pulled later. And so that is a reason and also the extra people would allow us to have these reviews in a much more timely way than we can do today and we think that the timely review plus just the value of having that FDA advisory review would encourage participation.

Mr. GREEN. In your opinion, is there a public health benefit or safety, drug safety, benefit on direct-to-consumer advertising for newly approved drugs?

Ms. MULLIN. Well, I am not an expert on that. I am certainly not a lawyer. But it is my understanding there are first amendment concerns related to that.

Mr. GREEN. Well, I guess I have some concerns in using Vioxx and I know when it was first developed, I actually had relatives wanting me to get them some because they thought it was getting prescription, because their illnesses and so the market was created for it. And I guess, maybe, if we are going to create this market, which is what advertising is for, we ought to make sure that that pharmaceutical does not have these side effects that we now know and of course, the civil justice system took care of some of that because we had this untold number of lawsuits on Vioxx. I would much prefer the FDA to do that and the pharmaceutical industry before people have to go to the courthouse. Mr. Chairman, thank you for the time.

Mr. PALLONE. Thank you. Mr. Murphy.

Mr. MURPHY. Thank you, Mr. Chairman. Just a couple of quick questions. One relates to the issue of dealing with the statutory time limit that restricts user fee funding for drug safety, I believe it is 3 years. How long do you think this should be extended? What would the cost of that be if it went beyond 3 years?

Ms. MULLIN. We are basically recommending that the time limit be altogether removed because I think, we believe when a safety issue comes up, you don't want to have an artificial restriction on what products can be included in the study, for example, that you might want to use user fee funds to support the work that is going into that analysis and you wouldn't want to leave products out of the analysis because of a date restriction. We have accounted for the removal altogether in the proposed amount of additional fees that we are talking about here.

Mr. MURPHY. Would this, then, allow you, for example, if a drug, drug *X* is used and it has begun to be prescribed for different pur-

poses, say, 3, 4, 5 years after it was first approved, this would allow you to go into other trials and other reviews of those medications once new discoveries would come up for those drugs?

Ms. MULLIN. Absolutely. We would continue to follow the product through the whole life cycle, as we say.

Mr. MURPHY. Thank you. And another area, this agreement, it establishes a new user fee for reviewing direct-to-consumer advertising. Now, some members would like to require review of all advertising, including print, Internet, television, et cetera. How would this work? Would the fees be sufficient to cover all levels for the FDA to review all advertisements and on all media?

Ms. MULLIN. No, the amount of money we are talking about here, the $6.25 million, was specifically to address the staffing that we thought would be needed to deal with just the more timely review of direct-to-consumer TV ads and we assumed that we would get more than today. We assumed that there would be about 150 submissions of such ads per year, that was a ballpark number we used to come up with the resources. It was not and did not include anything, any scope of work beyond that.

Mr. MURPHY. But we have to know that there are many levels of ads that, through print and magazines, there are multiple pages of ads; there are things, pop-ups on the Internet that also cover those. How will we review those direct-to-consumer ads and determine if they are appropriate?

Ms. MULLIN. We have a staff that review ads more generally will still be there. I mean, we will still be reviewing those ads as well as we can, all of the other materials.

Mr. MURPHY. I hope so, because it is an area that certainly many constituents are concerned about, with regard to the amount of funding that is spent on direct-to-consumer ads. If they influence a patient's decision when they come to physicians' offices and demand to be prescribed certain drugs, it is important that those ads do depict, in an accurate and truthful way, all those claims and I mean, I certainly understand the value of letting people know that there are medications available and they do have some benefits in terms of helping people understand that they may even have an illness that they are not aware of and that it is treatable.

However, we also want to make sure that they are not increasing unnecessarily prescription drug and healthcare costs in doing that, so I don't know if this is enough money to cover that. I am very concerned about all the other areas that are going on. I mean, if this is just television, it doesn't even cover radio, which there are several levels here. So I am very concerned and I hope that your efforts can be expanded to look carefully at all those areas.

Ms. MULLIN. Well, we will continue to look at those other areas, but this program, you are right, only focuses on, that we are proposing, only focuses on the direct-to-consumer TV ads for pre-review.

Mr. MURPHY. Thank you very much. Mr. Chairman, I yield back the balance of my time.

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

Ms. DEGETTE. Thank you, Mr. Chairman. Dr. Mullin, I have a concern that, as I said in my opening statement, that the public

has lost some of its faith in the FDA's ability to regulate the drug industry because of some of these high-profile problems that we have had and they believe, as a result of these problems, that the FDA has too cozy a relationship with the pharmaceutical and biotech companies. So to that end, I am concerned about these recent PDUFA negotiations that the FDA and drug industry have been having and the fact whether they were made available to the public. Can you talk to me about the negotiating process and what kind of public disclosure there was?

Ms. MULLIN. Our process, certainly. Our process began with a public meeting in November 2005 and we had a panel of consumers, a panel of patients' advocacy groups, a panel of healthcare provider professionals and academic researchers and also a panel from industry to begin with and to hear, sort of, the opening sort of view of the program and what needed to be addressed. We also undertook a lot of analysis within FDA to understand and sort of document what are the real issues to separate impressions that we may have from what the actual data suggest by way of the issues.

We followed it up with meetings with, a separate meeting with patient advocacy groups, a meeting in May with patient advocacy groups and a meeting in May with consumer advocacy groups and in June with healthcare professionals to further understand what their concerns were and hear about it. And they provided us with very helpful, I would say, kind of a big picture guidance about the areas of their concern. At the same time, we were having more detailed discussions with industry about things like rent and——

Ms. DEGETTE. And if you will excuse me, we only have 5 minutes. But those meetings were held privately, correct? With the meetings with industry. I mean, I know you had a couple public, opportunities for public input, but the meetings with industry were held privately, as I understand it.

Ms. MULLIN. Well, they were private in the sense of just industry people were involved in those discussions.

Ms. DEGETTE. Right. And so the question is in theory, those meetings could be held in public, similar to FDA advisory committee meetings? I am wondering, if you did that, is there confidential or trade secret material of individual companies that has been discussed in those private meetings with the companies? Is there some reason not to have more, to have the availability of the public, at least, sitting in on those meetings?

Ms. MULLIN. There is nothing confidential, commercial or trade secret, anything of that type discussed in such meetings.

Ms. DEGETTE. So what would be, given some of these issues and all of our concern that we restore the public's confidence, to the extent that it has been diminished, in the FDA, what would be the legal or policy decision to not have those meetings open to the public?

Ms. MULLIN. I don't know. I don't know how well that would work, but it is certainly worth looking at. I guess I feel that the most important thing we can do to restore public confidence is to get the program strengthened and so that is really, again, the sort of getting the resources needed. I mean, the workload I mentioned is a very difficulty reality and I think it——

Ms. DEGETTE. Right. Yes. And that is my next question, is the strengthening of the program that the FDA announced on January 30, I have got the press release here, talked about 41 separate activities, eight of which the FDA proposed to be funded out of PDUFA IV, and 18 as it described is recently initiation and 15 to be started. I am wondering how the FDA is going to find the resources necessary. I think it is a really ambitious and good strategy, I am just wondering how you are going to find the resources to fund it?

Ms. MULLIN. Some of these efforts involve better collaboration between pre- and post-market safety and that is one of the things that the program, overall, will be able to fund and in addition to the resources that we are talking about for PDUFA, we requested additional appropriated dollars and the president's budget includes $11.2 million in additional appropriated dollars.

Ms. DEGETTE. So the president's budget, the $11.2 million, would, if Congress appropriated that, would it be adequate to fund all of these improvements?

Ms. MULLIN. The ones that we described in our January response to the IOM report.

Ms. DEGETTE. Thank you very much.

Mr. PALLONE. Thank you. Dr. Burgess.

Mr. BURGESS. Thank you, Mr. Chairman. Dr. Mullin, thank you for being here and providing us with your testimony. The Food and Drug Administration is probably, when I think of Federal agencies, it is the Federal agency that I was very first aware of back in either the late 1950's or early 1960's, as a small child, reading the stories in Life magazine about the tragedy of phylitimite in Europe and whether it was because of bureaucratic inefficiency or scientific curiosity, phylitimite was prevented from being sold on the American market and we were spared that tragedy, so I am not sure that I can say that I was aware that it was the FDA that did that, but I was aware that there was a regulatory agency in the Federal Government that was looking out for the citizens in this country, but then that kind of morphed.

As a physician in the 1980's, I became very resentful of the FDA because it seemed like there were all these great things that were happening around the world and we could not get them for our patients. I didn't know that it was PDUFA that came along and allowed that process to be speeded up and allowed that backlog to suddenly begin to move forward, but is now the United States, where do we rank in terms of being a country that is able to get breakthrough pharmaceuticals to our patients in a timely fashion? Are we near the top, are we still in the middle or near the bottom?

Ms. MULLIN. We are definitely near the top. I think we are considered to be still the gold standard in terms of getting products to market and including safe, effective products to market. I think there is a recently considerable interest in Europe in trying to improve their support for new product development, to sort of work, you have probably heard the term we have used, critical path, but they have become very interested in that because of wanting to be more competitive, but we are still considered to be a world leader.

Mr. BURGESS. So have we, in a sense, traded places, then, with Europe since the 1980's where it seemed to take us so long in the

1980's to get new drugs to market and Europe could have them, essentially, as soon as they were off the laboratory branch, Europeans physicians had access to medications where we would have to wait, it seemed like, years. Have we now switched positions with Europe?

Ms. MULLIN. I believe we have. I haven't seen the most recent data, but it is my understanding that we are definitely a country that is often the first place in the world where a new product may be introduced and patients in the U.S. may have first access.

Mr. BURGESS. So largely because of the efforts that Congress made many years ago, 15 years ago, with the first PDUFA, with PDUFA I, that was able to alleviate some of that backlog and begin to break that log jam, was that?

Ms. MULLIN. We think that is a factor. We think that is an important factor.

Mr. BURGESS. Well, I agree with you and I think it would be a mistake to see it go away. Now, let me, you were asked a question about Dr. McClellan's comments on the use of information technology to speed the process or to essentially speed the learning process for drugs after they have gone on to market. Do you, at the FDA, now currently have the architecture, the infrastructure in place to allow you that sort of rapid learning environment from an information technology standpoint?

Ms. MULLIN. We don't have that infrastructure today and part of our proposal here includes some funding to improve the infrastructure for adverse event collection and also to link, to access linked databases, which are the type that are being referred to in that active surveillance concept.

Mr. BURGESS. And is that through PDUFA or is that through part of the general appropriations process?

Ms. MULLIN. Well, certainly in PDUFA we have tried to include that. Overall, we are trying to improve our IT infrastructure at FDA and generally trying to do that for all medical products and other products, as well, so I have to say that it is part of our larger budget effort, as well.

Mr. BURGESS. Am I correct in the assumption that that part of information technology infrastructure that is purchases through any funding available through PDUFA will not have any strings attached to it so that it has a particular drug's name on it as a product goes through?

Ms. MULLIN. There are no strings attached to it in that way and I also think it is an understanding, in terms of getting resources for drug and biologics infrastructure that with the same infrastructure is one we will want to build on for medical devices and other medical products. It doesn't make sense to have many separate systems.

Mr. BURGESS. I would agree with that philosophy wholeheartedly. Now, just for my own edification, what is the process for review? A new drug comes to market, is approved by the advisory panel and approved by the whole FDA, it becomes generally available to clinicians and patients throughout the country. Is there a defined period for look-back as to problems that might be surfacing? What are the procedures that are in place now for a new drug that comes to market?

Ms. MULLIN. Well, the new drug review process actually begins much sooner than when we get that marketing application; that actually marks sort of the end of the development phase. The first time FDA sees a drug is actually when an investigational new drug application is submitted, really is drug begins clinical trials in humans and we continue to get information about that product over the years of development. We have meetings with companies.

Mr. BURGESS. That database is then built upon by data that trickles back in after it becomes generally available to the local medical doctor and the patients in the community?

Ms. MULLIN. Right. Yes.

Mr. BURGESS. Did we used to just get a form to fill out, to say that if you have had a problem with a drug in the past year, fill in this form and do the best you can to recollect all the particulars and send it back to the FDA postage paid? I don't recall ever receiving any information or maybe it was just because I was inattentive and curious, but I don't ever recall receiving any information that said now we have got this up on the Internet and you can simply go to a secure Web site and record the same information. Somewhere along the line I stopped getting the prepaid envelopes, so again, maybe I just wasn't paying attention. Has that process been in place?

Ms. MULLIN. We are right now working on really simplifying and streamlining our med watch reporting process so that it is one entry point straightforward.

Mr. BURGESS. So can I still get those envelopes in the mail once or twice a year?

Ms. MULLIN. I actually don't know if you still get those in the mail, but we are trying to make the Internet based reporting much more straightforward.

Mr. BURGESS. I am about to run out of time. I will say I have never been a fan of direct consumer advertising. As a physician, I was always insulted when a patient would come, carrying a 3-year-old magazine and an ad and say I want this, Doctor, and I realize I shouldn't have left them in the waiting room so long that they had a chance to do that, but I am grateful that you are spending some time and effort to monitor that. I am grateful that there is going to be a pre-approval process. Of that one-third that now does not voluntarily pre-approve, I think you mentioned a number of one-third that doesn't go through the process, to what extent are you finding problems in that one-third that is self-unregulated?

Ms. MULLIN. Actually, it is one-third that do submit today for pre-review and advisory review.

Mr. BURGESS. Oh, OK.

Ms. MULLIN. And I actually don't know the percentage where we would recommend to them that they make some changes because we feel that the ad is not a fair and balanced representation of the benefits and risks. I do know, I have been told the top five reasons why ads are considered to be violative and they sort of are the overstatement, the understatement or the minimization or omission of risk information.

Mr. BURGESS. With the disclaimers they have to put on the television, I don't know why they even do it in the first place, but it is America and they are allowed free speech rights and I don't

think we, at least right now, if there was a way, finally, on the off-label use of medications, are you going to look at compiling a database for the off-label use of compounds, some of which is extremely valuable to clinical practice, some of which borders on quackery, but are you going to be watching and is that going to be something that is generally accessible to clinicians and providers?

Ms. MULLIN. I think, as we move toward this approach of active surveillance, which is what we intend to do through PDUFA IV, we are going to have the ability to look at the population database and how the drug is used and of course, that is going to include its use off-label, so it is going to give us a much more complete picture of how drugs are going to be used and we will be able to do a much better job of analyzing the ways in which they are off-label used.

Mr. BURGESS. Even if the manufacturer has no interest in pursuing the off-label——

Mr. PALLONE. We have got to move on here.

Mr. BURGESS. Let me give you that one in writing, because that is important. Some drugs do actually have a black box warning and for all the good they do, we go around that in clinical practice, but thank you.

Mr. PALLONE. Thank you. Mrs. Capps.

Mrs. CAPPS. I want to congratulate you, Dr. Mullin, for your recommendations to modernize your post-market review capabilities and shore up your work force for post-market safety work, but I notice that you only discuss how user fees would be used to achieve this. Now, I, along with several of my colleagues, are going to be urging for greater congressional appropriations for the FDA and for lessening the percentage of revenue that is relied upon from the industry.

I do take seriously the recommendations of the four former FDA commissioners who agreed that we would be better served through a greater direct appropriations which would give the FDA more independent authority and would lessen the reliance on constraining agreements with the industry. So I want to get on the record and ask you if you agree, and it can be a yes or a no, that if a greater percentage of FDA funding came from appropriations, from us, from the taxpayers, if you will, the agency could better provide for an independent drug review system?

Ms. MULLIN. Well, I have to say that I don't think that the share of resources that come from fees versus appropriations really has any effect on the regulatory decision process. There is no evidence of that. I wouldn't want to imply that we don't welcome more appropriations, but I don't see any impact on the regulatory decision process.

Mrs. CAPPS. Excuse me. No matter what the percentage is from the private sector?

Ms. MULLIN. I don't think that it affects the review process. I don't think that our reviewers, while the people who work in my kind of job, who are aware of budget and where the money is going and the financial analyst types may pay attention to that. We work in planning and budget offices. The people who actually do the reviews are in another part of the organization; they are focused on the review. And so I don't see that it matters to that process.

Mrs. CAPPS. I guess you can tell I am aligned with the four former FDA commissioners. But I will move on because I believe that the public understand that we need to be taking an effort to ensure that FDA retains independence when we have heard about so many instances of undue influence by industry, so whatever the percentage, surely there are concerns about undue influence and I want to ask you what steps you will be and perhaps already are taking to ensure independence?

Ms. MULLIN. Well, as I said, the appropriations side, the user fee side of the program has been adjusted over the years for inflation and workload and the same mechanisms haven't been there for the appropriations side, so that is why I think we have seen this continuing growth of difference between them. The people who do the reviews are in different parts of the organization. They are in the drug centers, they are in review divisions and they really are not aware of whether the money that is supporting them comes from user fees, appropriations. That is something that is actually determined after the fact. We figure that out at the end of the fiscal year what percentage we have had from user fees or appropriations.

Mrs. CAPPS. So the understanding that I have had, that there is a plan to exclude individuals from an advisory panel if they hold $50,000 or more in financial ties to the company or its competitor, that is only determined after the year?

Ms. MULLIN. The advisory committee issue that you are mentioning is not one in my area of expertise and it is really a separate issue, but I would be happy to get any questions you have about advisory committees answered by the people at FDA who are experts.

Mrs. CAPPS. I would like to have that. I understand that that is a plan and I am kind of disheartened to have read just last week about an advisory for Arcoxia, which did, even those this proposal is under say, that particular panel included scientists with financial ties.

Ms. MULLIN. Well those are not FDA reviewers. Advisory committee members are not FDA staff reviewers.

Mrs. CAPPS. No, but advisory panels are very influential, is that not true?

Ms. MULLIN. They give FDA advice and I think they are important and I would really want to take your question back and have it properly addressed in writing for the record.

Mrs. CAPPS. I was assuming that it was under your jurisdiction, but so I would really appreciate a response to this. I think there is some concern that I have held about the importance, and maybe that could be part of my question that you will get back to me or somebody will, about the role that the advisory panel plays, then, in determining the approval. Is it just advice and to what degree is it advice. Thank you. I appreciate that. And with that, I will yield back and wait for an answer.

Mr. PALLONE. Thank you. Recognize Ms. Blackburn.

Mrs. BLACKBURN. Thank you so much. Let us see where I want to start. Let us go back to Dr. Burgess' question where we were talking about the drugs that are approved in the country and how often in the U.S. we are first approved with new drugs that are

coming to market and we look at other areas around the globe and how often those drugs are first to market and available to our consumers here. I would like for you to expand on that just a bit and give us, if you can, percentages where we are first to market with new drugs or maybe even raw numbers and you can do this in writing.

You don't have to do it right now, but I think that that would be helpful for us and knowing how often that was the case prior to PDUFA so that we can look at some apples to apples comparisons, if you will. And then another thing I would like to know and maybe you can expand on this just a little bit. If PDUFA were not reauthorized, then the amount of time, the length of time that you would expect that review process to increase and delaying the patients' access to new therapies and new drugs. What kind of delay would we expect to see? And you may be able to answer that or you may want to submit that in writing.

Ms. MULLIN. I think we need to submit it in writing. The program currently is supported by actually, get the right number here, of more like 58 percent of the funding of PDUFA today comes from user fees; 58 percent from fees, 42 percent from appropriations. So as you can imagine, that would have, probably, a fairly devastating effect on the program. Fifty-five percent of the FTE support, slightly different, comes from user fees. So more than half of the people in the program, almost 60 percent of the funding of the program, which covers other things related to costs of the programs, so if that were to go away and rather abruptly, it would cause a lot of dislocation.

Mrs. BLACKBURN. Another thing I think would be helpful to us is to know specifically what policy changes, and you have talked a little bit about this in your testimony, but specific policy changes that would impede your success or your continued success and as you all talk about different things, throw that in as you write your response, just the specific actions in those policy changes.

One thing I do want to highlight. In reading your testimony and then listening to your answers, as we look at the reauthorization, I think it is important to all of us that, and it certainly is important to me, that any funding that you have, and we need to know if FDA is going to ensure that the funding reaches its intended targets and is not just used to increase the bureaucracy. PDUFA came about because of an unresponsive bureaucracy and I think that it is an imperative to constituents that we deal with that are dealing with your agency, that the funding reach those intended targets and I hope that that is not lost.

Ms. MULLIN. Speaking as someone in the office of the commissioner, who might be viewed as part of the bureaucracy part of that, we have actually tried to reduce the administrative overhead of the program to make sure we are hiring more reviewers with the money and really putting it where it is needed most in the premarket and post-market safety reviews.

Mrs. BLACKBURN. My time is going to run out and I have got two more questions for you. One, on your IT improvements, the infrastructure that you are building, are you doing that in-house or are you outsourcing that work?

Ms. MULLIN. Most of our IT work is done through contract work.

Mrs. BLACKBURN. Through contract, so it is outsourced. Do you consider it on-schedule or is it lagging behind?

Ms. MULLIN. I think it is on schedule and I think that we are paying a great deal of attention, because resources are tight, to making sure that those contracts are very well managed.

Mrs. BLACKBURN. And then I will just highlight your DTC program and the advertising review. I think we are all going to be watching very closely on the type expansion that you are looking for, the direct-to-consumer advertising is something that a lot of complaints come in about and as you move forward with a framework with basically your expectations, a clear definition of that, I think it is going to be something that we are going to be watching closely to see and I yield back.

Mr. PALLONE. Thank you. Ms. Hooley.

Ms. HOOLEY. First of all, thank you so much for testifying and taking all of our questions and sometimes I think we forget what an awesome responsibility you have, how important it is to get new drugs on the market, what it does for people's lives, how important it is to make sure when they come on the market they are safe and that you do that follow up. So I have some questions in regard to some of the follow-up. And thankfully, you are removing the 3-year time limit for post-market review. That means that you will obviously have a lot more work to do in your surveillance office.

In your written testimony you stated that the recommendations for PDUFA would permit the hiring of 82 additional staff for post-market safety activities. How many employees do you currently have working on that post-market safety? And what I am trying to do is get a better sense of how much this additional funding for post-market surveillance will get you; how many of the new hires in the post-market safety division would you estimate will be used in maintaining the existing level of post-market surveillance out past that current 3-year window versus engaging in new and more comprehensive surveillance activities. So that is sort of my first question. Let me ask the second and you can answer both of them.

It is my understanding that the Office of Surveillance and Epidemiology has little or no enforcement authority of its own. The Office of New Drugs has that authority. Do you think the Office of Surveillance and Epidemiology should be given more authority to act when it uncovers post-market safety concerns? If the expertise on post-market safety is within their office, doesn't it make sense for that office to have enforcement authority?

Ms. MULLIN. I think that, in FDA's view, it is FDA that has the authority and that we really work as a team and if we are talking about benefit and risk and you can't separate benefit and risk; instead of pre-market/post-market, we think you have got to combine the information you obtained about the drug pre-market with the further experience post-market and look at, again, benefit versus risk of a product and see whether the balance of benefit versus risk is adequately served by the current labeling and whether the drug should be on the market, but really, we like to think of it as we are trying to create a team here.

Talking about a culture of safety, we think the way, the best way to address this is to create a strong team across pre-market and post-market and not further look at divisions there. So I think that

we view it as benefit versus risk, life cycle of the product and let us keep focusing on learning and bringing the new information that we get into our overall assessment of the product. So that is kind of, I think, the approach we are trying to take and use the best science, also, in trying to update the information that we have.

You asked about numbers and I have—at least, I don't have the whole office here, but I do have some information about, at least, the fee supported part of post-market safety staff today and the fiscal year 2005, I have the actuals in front of me. We don't have the actuals yet available for 2006. That year just closed out last September.

Ms. HOOLEY. All right.

Ms. MULLIN. And the total FTE for post-market risk management funded by fees was 62 staff.

Ms. HOOLEY. So you would get an additional 82 over the 62?

Ms. MULLIN. That is correct.

Ms. HOOLEY. OK.

Ms. MULLIN. And that 62 is spread across the——

Ms. HOOLEY. And then how are you going to use that additional funding? You are going to hire 82 additional, so——

Ms. MULLIN. Well, first of all, you were saying a minute ago that taking the time limit away would create more work. And actually, the work, we think, will be the same. I mean, the workload is one thing; having the resources that we can apply to the workload is what we are going to be able to do now that we got the elimination of the what we can support with the fees, so we are going to be able to use those fee dollars to support the work that is there already. And we are going to spend about $5 million a year of contract epidemiology studies and we are going to be using about a few million dollars to do the IT upgrades that I have been talking about and the balance of the resources would be used for training our staff that are on board today, conducting a few public processes that we described in the testimony that I provided in writing and basically hiring more epidemiologists and safety experts so we can beef up our capacity. We need more people to do that work, as well as giving them better tools. So that is how we would use the resources.

Ms. HOOLEY. Thank you and I yield back my time.

Mr. PALLONE. Thank you. Mr. Pitts.

Mr. PITTS. Thank you, Mr. Chairman. Thank you, Dr. Mullin, for your testimony. A couple of things. As I understood your testimony, is the United States now the country where most new drugs are first approved?

Ms. MULLIN. The data that I have is not the most recent and the last thing I saw on this, and I think it is a couple of years old, so I would rather go back and get the latest analysis from our economists and provide that for the record.

Mr. PITTS. But we are certainly near the top?

Ms. MULLIN. We are certainly near the top.

Mr. PITTS. Now, was this the case prior to PDUFA?

Ms. MULLIN. No, it wasn't. Actually, there has been something of a reversal, if you look at the data going back.

Mr. PITTS. If PDUFA is not reauthorized, could we expect to see review times increase and thus delay patients' access to new therapies?

Ms. MULLIN. Yes, I think it would be safe to say that you would see that.

Mr. PITTS. Now, a goal of PDUFA IV is to accelerate the move towards automated drug review and improve health IT infrastructure at the FDA. How will that help reviewers analyze applications?

Ms. MULLIN. I think having better access to population databases will be extremely helpful, certainly as you get into post-market review it will help. But also, as we get information when an efficacy supplement comes in, that is a product that has been on the market for a while, so you have post-market experience with that as well as the new information that you will receive in an efficacy supplement. And so I think it would help both the pre-market reviewers and even more, the post-market reviewers in trying to get a more complete and accurate picture of the use of the product out there in the delivery system and trying to understand the adverse event reports and signals that we are getting so we can appropriately respond.

Mr. PITTS. Now, as I understand your response to Congressman Buyer, I think you said much of the 60 percent increase in adverse effects over the last 3 years can be attributed to counterfeit drugs on the market, is that correct?

Ms. MULLIN. No, I don't.

Mr. PITTS. No.

Ms. MULLIN. I think I said I don't know how much of that can be attributed. I really don't know how much of that could be attributed to the use of counterfeit drugs. The data on counterfeit drug use is pretty imperfect, but I don't know the amount. We can go back and get the best information we have on that for the record.

Mr. PITTS. What about foreign versions of FDA approved drugs?

Ms. MULLIN. A foreign version of an FDA approved drug, I am not expert in this area, but it is not an FDA approved drug if it is not the version that is used and labeled by FDA.

Mr. PITTS. What could Congress do to help you deal with counterfeit drugs or foreign versions of FDA approved drugs?

Ms. MULLIN. I don't think I can give you an adequate answer and we have experts at FDA who can, so I would rather take your question back to them and provide the answer for the record.

Mr. PITTS. Is there something that doctors need to do, that we need to ask of doctors to ensure that they are getting the drug from a supply chain which they can control?

Ms. MULLIN. Again, I would like to include that in the answer that we provide for the record.

Mr. PITTS. All right. Thank you, Mr. Chairman.

Mr. PALLONE. Ms. Eshoo.

Ms. ESHOO. Thank you, Mr. Chairman, and thank you, Dr. Mullin, for your testimony so far. An all-electronic drug review system at FDA, we know, is going to cut application time and decrease or entirely eliminate paper filing. And I think that those are two very important goals and I think that they need to be achieved. It is also very importantly, I think, a way to eliminate medical errors

and in time, it could help track safety information through a product's life cycle and it would be useful for data mining activates to identify adverse events and compile clinical trial data. So it clearly is a very important investment and it would produce a lot of outcomes that we need and that we are looking for.

Now, I understand that the administration's PDUFA proposal includes $4 million to move the FDA toward an all-electronic drug review system. Now, when you compare the $4 million with something else, $6.25 million that would be generated to support the new user fee for direct-to-consumer television ad reviews, it is a curiosity to me. So I want to ask you, in your view, is the $4 million adequate for the adoption of an agency-wide program for an all-electronic drug review system?

Ms. MULLIN. The $4 million is not adequate, but fortunately, and we should have made this clearer in my testimony, that that is in addition to what we are already spending from user fees on IT systems and so——

Ms. ESHOO. What is the total amount?

Ms. MULLIN. The total amount that we are currently for PDUFA, which we would continue to spend in going into the future and——

Ms. ESHOO. But I am asking you, what is the total amount for the all-electronic drug review system?

Ms. MULLIN. The total amount that we are spending from PDUFA fees would be more on the order of $34 million because we are spending about $30 million per year now from user fee dollars.

Ms. ESHOO. So the $4 million——

Ms. MULLIN. Is added on to about $30 million.

Ms. ESHOO. And will that complete, is that complete funding to achieve the system that I just outlined?

Ms. MULLIN. No, it is not and there are also, we are trying to build systems that are not just siloed for human drugs and biologics, but make it a system that can also be accommodating medical devices and other medical processes.

Ms. ESHOO. So $34 million is what? For this year?

Ms. MULLIN. The $34 million would be the amount that would start in 2008 if we had the $30 million going forward from PDUFA III added to $4 million from PDUFA IV. In addition to that, the $4 million that you are referring to is the pre-market component, but as you were saying, post-market——

Ms. ESHOO. Is it going to require an additional appropriation for Congress or are the user fees going to cover this?

Ms. MULLIN. For PDUFA and for human drug review, we are seeking these resources for user fee support and there is, in addition, the $33.7 million for post-market proposals IT support. So for in PDUFA, the new money we are talking about in PDUFA IV would be $4 million for pre-market, $3.7 for post, so that is $7.7 million new IT money in PDUFA IV on top of about $30 million a year we are spending currently for PDUFA user fees on IT.

Ms. ESHOO. I see. Now, can you briefly explain the steps that FDA is going to take under PDUFA IV to modernize and improve the ways that the post-market safety will be monitored and analyzed?

Ms. MULLIN. Certainly. We would begin by trying to improve our IT informatics support, as you were just saying. The collection of adverse event reports that are accessed to link databases——

Ms. ESHOO. So you are looking to have this system beef it up, essentially? It is relying upon this?

Ms. MULLIN. The infrastructure is an important piece, but in addition to the infrastructure, we are going to look at the best way to collect adverse event information so that we get the most information out of it, best epidemiology practices. We haven't got a standardized set of practices for those studies today and we want to have access to these databases. We want to make sure we use good methods to analyze the data once we have it, so increasing our access to population databases to be able to conduct studies of post-market——

Ms. ESHOO. Let me just very quickly ask, because I have 11 seconds left, what has FDA done to identify drug safety problems and remove products from market earlier in the post-market cycle? It is a problem for the FDA and this why the confidence, I think, of the American people has gone down.

Ms. MULLIN. Well, what I am able to talk about today is what we are trying to do going forward and beefing up the program and providing more resources to do a better job under the current authority and I think as Chairman Pallone just said, we will have the experts here for a separate hearing on drug safety and they can help with that.

Ms. ESHOO. That is fair enough. Thank you. Thank you, Mr. Chairman.

Mr. PALLONE. Thank you. And I recognize the gentlewoman from New Mexico.

Mrs. WILSON. Thank you, Mr. Chairman. So a financial report, I think it is the most recent one on PDUFA and there was a section in it talking about people and the challenge that the FDA faces in hiring, training and retaining qualified reviewers. According to the report, it said that the agency's ability to attract and retain the best and the brightest in medicine and science is critical to maintaining FDA's recognized gold standard in new product safety. It also notes that a large number of FDA's reviewers are nearing or entering retirement eligibility and they are also, many of them have excellent employment opportunities outside of Federal service.

Can you talk about that a little bit and the challenges that you face and whether the legislation that you recommended addresses this in any way?

Ms. MULLIN. Certainly. I think that it is a continuing challenge for FDA to attract and then retain people who, by virtue of their growing experience at FDA, become even more attractive to other employers and so it is a challenge to us. One of the things we provided for, I haven't said a great deal about, but in that sound financial footing piece, to try to increase the amount of inflation adjustment in which we include our payroll and payroll benefits.

And that includes that retention allowances for a lot of our very specialized scientific and medical experts so that we can attract people like that to come a little closer to the kinds of compensation they might receive elsewhere and cover the healthcare costs of the people in the program and retirement costs. So we are addressing

it by really catching up to and putting in a provision that will keep us able to cover those costs going into the future so that we can attract and retain those people.

Mrs. WILSON. What kind of retention bonuses are available for these kind of folks and what kind of base salary levels do they, on average, get?

Ms. MULLIN. I am not able to actually give you accurate details on that, but I would be happy to go back to the people who keep those numbers and provide an answer for the record.

Mrs. WILSON. Is there anything in the draft legislation that would address this issue of recruitment and retention of qualified personnel?

Ms. MULLIN. We address it through the change to the inflation adjustor where we say we would like to have a provision that includes the most recent 5-year payroll costs for the agency as another possible adjustor for inflation. That number has been running at 5.8 percent on average for us as opposed to 4.2 percent, which is the 5-year average for just the Federal pay raise. So this will help us to keep resources so that we can get to the numbers of these qualified people that we want to have and retain.

Mrs. WILSON. And are you having any difficulty at this point in keeping those positions filled or any difficulty in recruiting new qualified reviewers when you have folks retire and move on?

Ms. MULLIN. Not if we have the resources and not if, people have a sense that the program is going to continue, I think we will be fine.

Mrs. WILSON. But currently, do you have a large vacancy rate or a large mobility in your reviewer pool?

Ms. MULLIN. Well, now that we are going forward with our 2007 budget and able to move forward, I think we are going to be able to staff up and with the increasing resources we are proposing in fiscal year 2008 with PDUFA, we will really be able to aggressively try to fill the positions that we need to fill to get the program adequately staffed. We have actually experienced a loss of FTE because of other costs going up. We haven't been able to afford as many people in the most recent years of the program, so we are trying to address that so we don't lose people because we are having to take the money to pay rent or rent related costs and that kind of thing, so we think we will be in good shape going forward.

Mrs. WILSON. Thank you, Mr. Chairman.

Mr. PALLONE. Thank you. I recognize the gentlewoman from Wisconsin.

Ms. BALDWIN. Thank you, Mr. Chairman. Thank you, Dr. Mullin, for your testimony. There has been a fair amount of discussion in the questions about public confidence in the FDA and various ways in which it may have been eroded and how we can bolster that. And Congresswoman Capps asked some questions about the advisory panels and financial conflicts of interest that might exist and you are going to refer those questions to colleagues of yours. I would like to take a closer look at the question of political interference rather than financial conflicts of interest that might be experienced by the scientists who are employed by the FDA.

In response to a previous question, I think you were indicating that the balance of private sector versus taxpayer dollars doesn't

influence the research because they are employed in a separate division, et cetera. But you are probably aware of last year's Union of Concerned Scientists' survey of FDA scientists and concerns that were raised in their report about political interference with science and as I reviewed just an executive summary of this, it appears that the survey was provided to or the opportunity to fill out the survey was provided to nearly 6,000 scientists.

About a thousand, just a little fewer than a thousand participated in this survey and there were some pretty disturbing findings. There were some open ended questions and also limited answer questions. One in five responded that, the scientists responded that they had been asked for non-scientific reasons to inappropriately exclude or alter technical information about their conclusions in an FDA scientific document. More than three in five, 61 percent, knew of cases in which the Department of Health and Human Services or FDA political appointees had inappropriately injected themselves into FDA determinations or actions.

Three in five said they knew of cases where commercial interests have inappropriately induced or attempted to induce the reversal, withdrawal or modification of FDA determinations or actions. And 50 percent also felt that non-governmental interests had induced or attempted to induce such changes. In another area it says nearly 70 percent of the respondents to the survey do not believe the FDA has sufficient resources to effectively perform its mission of protecting public health and helping the public get accurate science-based information they need to use medicines and foods to improve their health.

On the open ended question that was posed, a couple of quotes that I found particularly distressing. One was, and this if from a scientist from the Center for Drug Evaluation and Research. "Scientific discourse is strongly discouraged when it may jeopardize an approval. Whenever safety or efficacy concerns are raised on scientific grounds, these concerns are not taken seriously." Another one, this one is from the Center for Devices and Radiological Health. This is a good quote. "In my experience, it is never the low level reviewers in the FDA who breach the integrity of our work. It is usually at much higher levels, such as center directors and above. Those higher levels are so far removed from the scientific work that we do, that politics has even more sway over their decisions. The people I work with are truly dedicated to serving the American public and doing whatever is in their power to ensure their safety."

And I have just several follow-up questions to what I have just iterated. One is, do you take exception to these results or if you don't, how is this reflected in your planning and budgeting, your response to this reflected in your planning and budgeting? And then back to the answer you provided earlier on the separation of the scientists from the budgeting decision making, how does that work at the upper levels where that separation, perhaps, isn't as strong and a number of the people who responded to this survey are indicating that the interference, the political interference is higher up?

Ms. MULLIN. OK. Well, let me begin by saying that I think that that separation goes all the way up. I don't think that anybody at

FDA, any scientist at FDA makes decisions based on the percentage of fee versus appropriated dollars. That is my belief. I think that first of all, one of the findings that you mentioned was resources and certainly with PDUFA, we have endeavored to address that as well as we can because we think that our review staff really does, they are overworked. I mean, they have a huge amount of work to accomplish and it is extremely important complex work and so what we have endeavored to do with PDUFA IV is really boost the resources to give them enough people to be able to do their job and because we fully support them and they are very dedicated people. Everybody at FDA, I think, is very dedicated.

The other point I would make is I think Dr. von Eschenbach is very concerned that, to the extent that people feel the way described in that survey, that that be addressed. And so I know that on his short list of his agenda and leadership priorities is to strengthen the environment of trust and transparency and integrity, to have everybody feel that the agency invites and we engage in vigorous debate on issues, but that we make science-based decisions within our regulatory authority and I know that that is one of his key elements of his agenda at FDA, so I think that our new leadership plans to address this very aggressively.

Ms. BALDWIN. I wouldn't ask you to speak for Dr. von Eschenbach, who isn't here today, but what you just indicated was almost, it sounds like you take issue with some of the things that I read, that there is a disbelief that the politics is actually getting involved in the decision making and that it is all science-based and yet your scientists don't believe that. I guess I am asking you has the agency decided to take issue with this study and its findings or are you acting purposefully to root out the politicization of the process as it may exist?

Ms. MULLIN. Well, I think we are trying to listen to what people's concerns are. I can't speak for the commissioner, but I would say that from what I can tell, we are trying to listen to the concerns and be sure that we are employing the best science in our decision making, that we have enough people to do the job and that we provide an environment that encourages debate.

Mr. PALLONE. Thank you. The gentleman from Michigan, Mr. Rogers.

Mr. ROGERS. Thank you, Mr. Chairman. I appreciate it. We have a very difficult job, Doctor. We had one of the most emotional cases I had in my office was a constituent whose wife was dying of cancer and firmly believe that there was a drug that was going through the final stages of approval, if they could only get that drug it might, in fact, save his wife's life and we worked as hard as we could to find some legal remedy that they could go around the system to be able to use those drugs, even knowing what the risks were and we couldn't, unfortunately, do it in the course of time.

And on the other side, I have a constituent who is no longer able to take a drug that has been removed from the market that brought her extensive relief and she didn't have the adverse effects that allowed that drug to be removed from the market and wants to find a way to be able to continue to access that drug for her health and care and this is a difficult, difficult thing for all of you to do and we appreciate how complex this issue is.

Your position is, in the FDA, for planning, is for the safety and efficacy, right? You come up with the system and the standard which allows us to go through the process so that you can, with some sense of surety, say that this drug is safe and it will do what we say it is going to do. Is that correct?

Ms. MULLIN. No, that is actually not quite right. I work at a much more, sort of, less close to the science level. I am in the office of the commissioner. We deal with issues across the whole agency in terms of budget and performance and provide that analysis that PDUFA involves; centers for drugs, biologics. Some work in the part of the field staff and the office of the commissioner.

Mr. ROGERS. So you are not a policy person to that degree?

Ms. MULLIN. I am a planning and analysis person and I am not a scientist and so the kind of——

Mr. ROGERS. But am I incorrect in saying that you are, at least, responsible for coming up with the template for how Drug A hits the FDA and at the end of the day ends up on a pharmacist's shelf, the process of that, not necessarily the science of that?

Ms. MULLIN. No, I am not responsible for that. The scientific staff within the centers of drugs and biologics really would determine what that process needs to look like. And it would be based on the scientific information that you need the evidence of safety and effectiveness. My job has been to try to help them figure out what resources would be needed to have an effective process, what kind of performance they want to specify to make the process run as efficiently as possible.

Mr. ROGERS. So they would come to you and say we need resources for *X* or *Y* or *Z* in order to accomplish what we believe is the right——

Ms. MULLIN. And they would have to detail what it is that needs to be done.

Mr. ROGERS. OK. So you at least, you have some visual into that process?

Ms. MULLIN. Yes, but it is, I would have to say, at a pretty high level.

Mr. ROGERS. OK. Because what concerns me is the World Health Organization estimated by 2003 that there were $32 billion of counterfeit drugs in the world market, which is about 10 percent. And in the U.S. value of counterfeit drugs seized in 2003 was $200 million, which was a sevenfold increase in the year before. So when we look at a 60 percent increase in adverse effects between 1999 and 2003, in a sevenfold increase in counterfeit drugs between 2002 and 2003, I used to be an FBI agent and scratched my head a little bit, but that is a clue.

There is a problem growing here and I don't get a sense, at all, that the FDA—and how do you go through an efficacy plan when a doctor is writing in that gee, that drug didn't have any affect at all on my patient? Matter of fact, just down from my office in Lansing, Michigan, they did a raid in the Detroit area and found that insulin was not refrigerated correctly, wrong instructions were on the drug. This is one of those Canadian pharmacies that we found out was not a Canadian pharmacy. And non-active ingredients. So none of that, according to the testimony I have heard today, gets factored in at all.

How can we honestly say we are coming up with a system for safety and efficacy even with post-approval, when we have no clue where the logistics chain of those drugs are?

Ms. MULLIN. Well, counterfeit drugs are an important concern. I think there are a lot of factors that could be cited that may be contributing to the increase in the number of serious and unexpected adverse events and that may very well be one of them. There are others, as well. For example, people are using a lot more drugs and people are using a lot more combinations.

More people are using more drugs at the same time, as well as perhaps dietary supplements and other things, so it is a complex picture, but I think what will help here is getting to the ability to go to these bigger population databases because we are going to be able to take a better look at the adverse events. I mean, as you say, some of those events could be caused by counterfeit products, but if we try to take a better look at when those events occur, we will get a better sense of what is driving it and the many factors that may be driving it.

Mr. ROGERS. But that is the only thing that concerned me, and I know my time is up, Mr. Chairman, is that that hasn't been already ruled in and how you would make that determination. Just in one port, they found that 85 percent of the packages they inspected, 85 percent that were labeled as Canadian drugs were, in fact, not Canadian drugs. That is a huge problem. And if you don't have a plan to roll that in to make that determination, maybe it is a 1 percent problem, maybe it is a 90 percent problem. The thing that scares me most is that you don't know.

Ms. MULLIN. Well, we do have a whole separate plan, if you will, related to imported products and it is not just in the drugs area, but across the whole range and we need a solution and informatics is part of that solution, as well, but I hear and we will be coming back with the answers for the record on counterfeit drugs. We will try to address the issues that you have raised. As I said, today a lot of the compliance work that would be involved in FDA's enforcement of counterfeit products is outside the scope of the PDUFA program.

Mr. ROGERS. Thank you and I yield back your time, Mr. Chairman.

Mr. PALLONE. Thank you. Mr. Stupak.

Mr. STUPAK. Thank you, Mr. Chairman, and thank you for allowing me to sit in and ask a few questions. As chair of OI, we have had two hearings on PDUFA reauthorization. Unfortunately, we look at the problems that continue to plague the FDA and unfortunately, I haven't heard anything that would assure me that the FDA's going to do anything different to improve the drug safety. If you take what Mr. Rogers was just asking you about, 10 years ago, Mr. Dingell and I did a bill on Internet sales, pharmacies, where we didn't have a big problem like we have now. I have been to those mail houses, as he has indicated, and for 10 years now we have been trying to get the FDA to even comment on our legislation and they refused and have not. Are you prepared to comment on it today, the legislation we have had on Internet pharmacy sales?

Ms. MULLIN. No, I am afraid not. I am not able to do that.

Mr. STUPAK. OK. You mentioned the 288 meetings you have had with drug manufacturers that your folks at FDA do. How many of those—were nine meetings a day, I think you said. How many of them dealt with post-marketing issues?

Ms. MULLIN. Most of those meetings that were talked about are dealing with issues during drug development, so they would——

Mr. STUPAK. But post-market——

Ms. MULLIN. No, they would not be post-market meetings.

Mr. STUPAK. So it sounds like you are more concerned about drug development, but not post-marketing safety surveillance.

Ms. MULLIN. In the program to date, the funding for post-market mismanagement work has been limited and so one of the things we are proposing for PDUFA IV is to get rid of that limitation on how long and how the funds can be used.

Mr. STUPAK. Well, I heard you say that and in response to Mr. Waxman, because I have been watching this hearing up in my office, if the FDA's primary mission is to ensure safety and efficacy of products proposed for marketing, is it to help speed it to market or to make sure drugs are safe and you said well, it is a dual or equal concern of the FDA, I believe you said, right?

Ms. MULLIN. Yes. I mean, we like to prevent problems before the products go on the market, too.

Mr. STUPAK. Then why isn't post-market surveillance, then, receiving equal amount of resources to do the post-market surveillance? Because if you have $29.3 million, that is about 7 percent of the user fees paid for post-market surveillance.

Ms. MULLIN. Well, the post-market surveillance piece is a little bit larger than that because we have money we are spending today on the order of about $15 million in the fee program today, so it would be added on top of that.

Mr. STUPAK. PDUFA IV reauthorization proposal is $29.3 million.

Ms. MULLIN. Right.

Mr. STUPAK. And that was what you developed this in consultation with industry.

Ms. MULLIN. Right.

Mr. STUPAK. So if my figures are right, that is near 7 percent of the user fees.

Ms. MULLIN. But those are added on to the base program that we have today and the base program we have today has about $15 million a year that goes to that purpose. The other thing I would say——

Mr. STUPAK. Fifteen million dollars, maybe another 3 percent; now we are up to 10 percent. Do you think 10 percent is equal to 90 percent?

Ms. MULLIN. Post-market surveillance is one component of post-market safety and——

Mr. STUPAK. Well, let us go to another component. Let us go to the 1,200 post-marketing studies that are pending before the FDA. Of those, 11 percent are done. 71 percent of the post-market surveillance that are supposed to be done have never been done, 71 percent. Why isn't the FDA demanding that the manufacturers do the post-marketing studies that they promised to do with the approval of these drugs? That is using your authority to get them to

do the post-marketing things, so we can leave money out of this equation.

Ms. MULLIN. Well, we don't have the authority to require, under current authority we cannot require the completion of those studies.

Mr. STUPAK. So what recommendations do you have to get the authority to require the marketing be done?

Ms. MULLIN. We are not recommending changes.

Mr. STUPAK. You are not making any recommendations, right.

Ms. MULLIN. We are not making changes in our authority. We are recommending that the increase——

Mr. STUPAK. So if you are not going to recommend any changes, how is this ever going to be resolved? You don't want the authority, you are not asking for the authority, so how are these 71 percent of 1,200 post-marketing studies that should have been done that are not done, how are they going to get done if you don't ask for the authority and you have no intention to ask for the authority?

Ms. MULLIN. Well, we include in our proposal for PDUFA IV is increased resources so that we can have the discussions of labeling and post-market commitments weeks before the action date and not what sometimes happens, days before. And we think the result of that is going to be much better designed trial that we expect actually would be completed at a higher rate.

Mr. STUPAK. How about the 1–800 number we talked about, post-market surveillance, and you rely upon the public, when the drug is finally being used, the public to help you with to flag problems with it? In the last PDUFA reauthorization, the FDA was supposed to put a 1–800, I believe it is FDA 1088 number on all bottle of medicine being prescribed. It has been almost 5 years. You still haven't done it. I have asked everyone from the FDA. They keep telling me it is going to come soon. Are you going to do this before the reauthorization, before September, or is this something I will have to once again stick in PDUFA so the American people know how to report an adverse event to the FDA?

Ms. MULLIN. I am not able to address that, Mr. Stupak. I don't know. We are working on a better Med Watch Plus, as we are calling it, online system.

Mr. STUPAK. I don't care about that. I want to know about the 800 number. I mean, when something happens, people don't know who to turn to, how to report an adverse event. You rely upon those adverse events to see if there is a signal out there, whether there is a problem with the drug.

Mr. PALLONE. If you could answer that and then we are going to move on.

Mr. STUPAK. I am sorry.

Ms. MULLIN. I would be happy to go back and to talk to the folks who know more about that and to provide you an answer for the record.

Mr. STUPAK. Same answer for 5 years, Mr. Chairman.

Mr. PALLONE. I understand. Thank you. And that concludes our questions, but thank you very much. We really appreciate your being here this morning. Thanks.

Ms. MULLIN. Thank you.

Mr. PALLONE. I would like to have the next panel come forward, if you would. Well, thank you for being with us, I was going to say this morning, but it is this afternoon. Let me introduce each of the five panel members from my left to right. Dr. Alan Goldhammer is deputy vice president for Regulatory Affairs for PhRMA. Next is Mr. Hubbard, William Hubbard, who is a senior advisor of the Coalition for a Stronger FDA. And then we have Mr. James Thew, who is a patient advocate with the ALS Association. And then we have Kay Holcombe, who is senior policy advisor for the Genzyme Corporation, former staff member for our committee. And next to her is Bill Vaughn, who is a senior policy advocate for the Consumers Union, a former staff member with Mr. Stark. So thank you all for being here and I guess we will start with an opening statement by Dr. Goldhammer.

STATEMENT OF ALAN GOLDHAMMER, DEPUTY VICE PRESIDENT, REGULATORY AFFAIRS, PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA

Mr. GOLDHAMMER. Thank you very much, Mr. Chairman and members of the Subcommittee on Health. I am Alan Goldhammer, deputy vice president for Regulatory Affairs at PhRMA. Having participated in each of the four previous user fee negotiations, I bring to the subcommittee today an historical perspective of PDUFA and the need for expeditious reauthorization. Last year FDA and industry representatives spent 9 months integrating comments from public stakeholders in discussing how the PDUFA program could be improved to continue to meet FDA's central mission of protecting and promoting the public health.

The passage of PDUFA in 1992 brought about tangible results in a very short period of time. Drug reviews that were averaging over 30 months were shortened and the backlog of pending applications eliminated. This added predictability to the drug review process and provided widespread public access to important new therapies. The 5-year sunset provision of PDUFA has been a good thing. It provides necessary time to gauge the effectiveness of the program, allowing all stakeholders to reflect on what can be further done within the confines of user fees to improve the review process.

The past two PDUFA reauthorizations have increased FDA resources, improving interactions during drug development, the information technology infrastructure and also and perhaps most importantly, FDA's drug safety operations. Throughout the past 15 years of PDUFA, the exacting standards by which FDA evaluates new drug applications has not been compromised. Increased resources have allowed FDA to complete its rigorous reviews more efficiently. The outcome of an individual review is not affected by PDUFA funding and whether a drug is to be approved is a decision for FDA alone to make based on information in the license application.

The PDUFA IV proposal being considered here today contains important new provisions and resources to enhance and modernize the FDA drug safety program, add a new user fee program for reviews and advisory opinions on direct-to-consumer television advertisements, improve drug development and provide a more stable financing for the program. We believe that the substantial new funding provided to enhance and modernize FDA's drug safety system,

nearly $150 million over the next 5 years, will continue to assure FDA's pre- and post-market safety assessment as the world's gold standard.

Furthermore, this PDUFA agreement substantively addresses all relevant recommendations in the IOM drug safety report that could be addressed through additional resources. These additional resources will be used to reduce FDA's reliance on the spontaneous reporting of adverse events and increase the use of modernized techniques and resources, such as epidemiology studies on large medical databases to identify risks more quickly and more importantly, accurately. FDA and industry also need a process to identify risk management, risk communication tools that are effective and work. This PDUFA agreement provides resources to accomplish this.

A key patient safety initiative is the allocation of a portion of the funding to improving the trade name review process. FDA will now have resources to review trade names during drug development, reducing the likelihood of medication errors because of confusing trade names. The proposal also includes a new user fee for reviewing the issuance of an advisory opinion on direct-to-consumer advertisements. In 2005 PhRMA issued a set of voluntary guiding principles regarding DTC advertising. Our member companies committed to submit all new DTC television ads to FDA prior to public dissemination to ensure FDA's suggestions could be addressed before the ad was aired.

This proposed user fee will ensure that FDA has the resources to review TV advertisements in accordance with our guiding principles. The proposal also suggests additional improvements to the drug review process. By implementing the good review management principles formulated during PDUFA III, FDA will communicate to sponsors the timelines for discussing labeling and post-market commitments in advance of the action date. This will lead to more meaningful post-market studies that are appropriate for the new drug.

Funding is also allocated for the purpose of expediting drug development. This will permit FDA staff to participate in external activities, such as partnerships and consortiums that are generating data and information that will create new paradigms for drug development. In return, FDA commits to developing draft guidance in areas related to safety assessment, clinical trial design and the use of biomarkers. This important work will lead to earlier patient access of important new therapies.

Finally, there are a number of proposed technical adjustments to the financing of the PDUFA program over the next 5 years. It is PhRMA's hope that collectively these will provide the sound financial footing needed to continue to keep FDA's drug and biological review program strong. And thank you.

[The prepared statement of Mr. Goldhammer follows:]

Statement at the House Committee on Energy and Commerce Subcommittee on Health Hearing on the Prescription Drug User Fee Act

April 17, 2007

Alan Goldhammer, PhD
Deputy Vice President, Regulatory Affairs
Pharmaceutical Research and Manufacturers of America

Thank you Mr. Chairman and members of the Subcommittee on Health. My name is Alan Goldhammer, Ph.D., and I am the Deputy Vice President for Regulatory Affairs at the Pharmaceutical Research and Manufacturers of America (PhRMA), a trade association representing the leading research-based pharmaceutical and biotechnology companies. PhRMA members alone invested an estimated $43 billion in 2006 in discovering and developing new medicines. We thus have a keen interest in ensuring that the Food and Drug Administration (FDA) has adequate resources to perform its critical functions of ensuring the safety, effectiveness and availability of new medicines for American patients.

Having participated in each of the four previous user fee negotiations, I bring to the Subcommittee today a full historical perspective of the Prescription Drug User Fee Act (PDUFA) and the need for expeditious re-authorization. Last year the Food and Drug Administration (FDA) and industry representatives spent nine months integrating comments from public stakeholders and discussing how the PDUFA program could be improved to continue to meet the FDA's central mission of protecting and promoting the public health. The outcome of those discussions will be the focus of my testimony today.

Reauthorization of PDUFA is one of the more important legislative issues facing Congress this year. Since its enactment in 1992, PDUFA has brought about tangible benefits to patients, the FDA, and the pharmaceutical industry. FDA's appropriated resources have been augmented by industry user fees, providing the Agency with sufficient resources to conduct reviews of new pharmaceuticals in a thorough and timely manner assuring widespread patient access.

It is important to put the PDUFA program in historical context. Initially it was unclear whether the program would succeed or not. Thus, the legislation contained a five year sunset provision. This has worked well, providing the necessary time to gauge the effectiveness of the program, and allowing all stakeholders to reflect on what can be further done within the confines of user fees to protect and promote the public health, the central mission of FDA.

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 (even though the statute calls for a 6 month review time), 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 eliminate 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.

In PDUFA-II, the program was enhanced by increasing FDA resources in return for improved interactions during the drug development process. PDUFA-III addressed FDA's needs for sound financial footing and increased resources that could be directed towards drug safety. Both of these reauthorizations also directed funding towards information technology infrastructure so that both FDA and industry could realize the benefits of electronic regulatory submissions.

Throughout the PDUFA programs of the past 15 years, the exacting standards by which FDA evaluates NDAs have not been altered. What has been altered is the level of resources available for FDA to perform its critical function of reviewing safety and effectiveness of potentially life-saving medications. With more resources provided by PDUFA, FDA has been able to complete its rigorous reviews more quickly and efficiently. The outcome of this review, however, is not affected by PDUFA funding and, depending upon the scientific data, may be a decision to approve the drug or to *not* to approve the drug. That decision is FDA's based on the information in the license application. User fees are not earmarked for specific applications and certainly are not contingent upon approval of the drug. They go into FDA's general budget and simply are used to hire additional staff to allow FDA to perform its critical drug review functions while maintaining the same exacting standards for safety and efficacy.

Furthermore, each reauthorization has focused on issues critical to the FDA's mission. Enhancements to PDUFA have always been carefully structured, responding to both the Agency's and the public's needs so that access to important new therapies is not impaired but in fact facilitated.

The Agency's PDUFA-IV proposal is no exception and contains important new provisions and resources to:

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

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

The substantial new funding provided to enhance and modernize the FDA drug safety system – nearly $150 million dollars over the next five years – will continue to assure that FDA's pre- and post-market safety assessment system is the world's best. When the Institutes of Medicine (IOM) report on the US drug safety system was issued last fall,

the recommendations applicable to PDUFA were carefully examined. I believe that this PDUFA agreement substantively addresses all relevant recommendations that could be addressed through a combination of user fees and guidance development.

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

The FDA's PDUFA proposal also provides funds to allow FDA to develop guidance on best epidemiology practices that will serve as a base for agency, academia, and industry use. This guidance is intended to serve the public's interest by assuring that studies reporting drug-associated signals of risk do so based on defined minimum scientific standards. FDA and industry also need a process to identify risk management and risk communication tools that are effective. Industry will benefit by having a list of risk management tools that work, simplifying the development of drug-specific risk management plans. Nobody wants to spend time and resources on approaches that will not benefit patient care. This PDUFA agreement provides resources to accomplish this.

Significant resources are spent by companies late in a drug's life cycle monitoring for adverse events. It is rare that significant new safety issues are identified this late and such resources could be better allocated to other drug safety activities. FDA will also conduct research during PDUFA-IV to determine the best way to maximize the public health benefit associated with collecting and reporting adverse events. We hope that this will lead to a better deployment of resources.

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 direct-to-consumer television advertisements. In 2005, PhRMA issued a set of voluntary guiding principles regarding direct to consumer advertising. In those guiding principles, PhRMA member companies committed to submit all new DTC TV ads to FDA prior to public dissemination to ensure that FDA's suggestions could be addressed before the ad was seen widely by the public. The proposed new user fee would ensure that FDA has the resources to review TV advertisements voluntarily submitted to FDA in accordance with the guiding principles and thus demonstrates the industry's commitment to those principles and to vigorous self-regulation.

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

post-market studies that are appropriate for the new drug.

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

Finally, it is important that we continue to assure that FDA is appropriately funded through a combination of appropriations and user fees so that the drug review program can address America's public health needs with the development of new medicines. A considerable amount of time was spent looking at increased workload within FDA, how it is measured, and how an appropriate workload adjuster can be constructed. This will provide the sound financial footing needed to continue keeping FDA's drug and biological review program strong throughout the PDUFA IV years.

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. We urge you to reauthorize the PDUFA program in a timely manner for the benefit of FDA, the industry and, most importantly, patients.

Mr. PALLONE. Thank you, Doctor. And next we have Mr. Hubbard.

STATEMENT OF WILLIAM HUBBARD, SENIOR ADVISOR, COALITION FOR A STRONGER FDA

Mr. HUBBARD. Thank you, Mr. Chairman. I have a written statement, but I will just make a few remarks, if I may. I am here representing a remarkable coalition of patient, consumer and industry groups that is trying to point out to the Congress that dire shortfalls at FDA resource problems are emerging. I was at FDA for 27 years, the last 14 in which I was an associate commissioner, very much involved in the origination of PDUFA and its most recent reauthorization.

When I came to the FDA in the 1970's, it was clearly the biggest problem that FDA had. Successive FDA commissioners and agency secretaries made it their highest priority. The patient groups were crying out for access to new drugs. Many patients were going overseas for therapy. We all remember the case of Rock Hudson going to Paris for AL721. Industry was very frustrated and feeling the standards might have to be lowered to get their products through the system. Research and development for new drugs was moving overseas to Europe and with lost jobs and lost ownership in pharmaceutical development. And then FDA was a much beleaguered agency in terms of drug review at that time.

Many things were tried during that period by commissioners and secretaries and others, administrative and regulatory reform through the 1960's and 1970's and 1980's and nothing seemed to work until this committee grabbed the reins and developed the PDUFA paradigm that exists now. So thanks to PDUFA, American patients now get drugs. First, the review process gets them products as fast or faster than anywhere in the world. Pharmaceutical research and development moved back to the United States and it stayed here in the years since PDUFA was enacted. And FDA has now had the resources to maintain the safety standards that you told them to maintain when you gave them the additional resources.

So I believe PDUFA is arguably the most important thing this committee has done, in the FDA context, since the 1938 Food, Drug and Cosmetic Act was enacted. But there is a downside, Mr. Chairman, to PDUFA. While the new resources have flowed into the program, appropriated funds have not kept up. That has caused two negative outcomes. First of all, industry fees are now an ever-increasing percentage, raising fears of undue industry influence, and funds have been shifted because of PDUFA, from pulling FDA programs elsewhere in the agency to the Drug Review Program, thus weakening public protection elsewhere.

I have one slide that I will ask to be put up very quickly to give you an example, a data example. If we could put up a slide called FDA Staffing. As you know, FDA does all of its work via its people and so I think this slide will demonstrate to you that while the overall FDA workforce is growing, the workforce for the programs other than users fees have declined. Have we got that slide or should I proceed?

The point of the data, Mr. Chairman, is that the increase in PDUFA has caused a concomitant reduction base programs at FDA, so that the agency's drug safety, food safety and other programs have lost a thousand people in the last 10 years, and we could explain that more at another time if you like. And so if I may, at the close, there are two big things I would hope that the committee would turn to next. One is on the drug safety side. The ledgers become imbalanced. All of these resources have flowed into the drug review side but at the expense of the drug safety side. And I have another piece of data that we can give you later that shows the tremendous increase in adverse drug reaction reports that the agency simply cannot look at, and I don't believe the current new PDUFA deal will substantially affect that, because the people that review that are not being beefed up substantially, so there needs to be more resources overall into the drug safety side to catch up with that huge increase on the drug review side.

And then the other thing that is going on is that while drug reviews have dropped substantially since the early 1990's, total drug development time still takes 10 to 12 years and there is great frustration on the patient and industry part, that these drugs are not getting through the system. FDA has a proposal to shorten drug development time so that from the initial synthesis in the lab to actual availability to doctors in writing their scrip, that can be shortened substantially. It is called a critical path. FDA has not been able to get the funding for that program and so I believe that there needs to be some way found to find additional funding for drug safety and for drug development that would compliment the progress made by the PDUFA program. So with those comments, I will end my comments. Thank you, Mr. Chairman.

[The prepared statement of Mr. Hubbard follows:]

STATEMENT OF WILLIAM K. HUBBARD

Mr. Chairman and members of the Committee, I am William K. Hubbard. Before my retirement after 33 years of Federal service, I served for many years with the U.S. Food and Drug Administration, and for my last 14 years was an FDA Associate Commissioner responsible for, among other things, FDA's regulations and policy development. Although I have remained retired since my departure from FDA in 2005, I have agreed to provide advice to a remarkable group of patient, public interest, and industry groups that have recently formed themselves into a Coalition for a Stronger FDA (whose mission is to urge that FDA's appropriations be increased). Throughout my career at FDA, I was deeply involved in improving one of FDA's most important functions—the review and marketing approval of new pharmaceuticals. Accordingly, I wish to thank the Committee for inviting me to testify on the Prescription Drug User Fee Act that the Committee is considering for reauthorization.

BACKGROUND

As you know, the process for assessing new drugs for approval is a complex and challenging undertaking. In any one year, FDA must oversee thousands of drugs undergoing testing, and review hundreds of applications to market the drugs that emerge successfully from the testing process. FDA's scientists have very little margin for error, as the approval of a new drug makes it available to millions of Americans, and often also triggers approval in many other countries, thus exposing any given drug to a potential patient population in the billions around the globe.

When I began my career at the FDA, the review of new drugs was the most troubled program in the agency, and remained so for many years. The signs of distress were rampant:

• Applications to market new drugs often lingered three or more years in the FDA review process;

• Patients pleaded with FDA for more rapid access to new therapies, particularly for serious and life-threatening illnesses, and sometimes felt compelled to travel overseas for therapy they could not get in the United States;

• Drug sponsors were increasingly frustrated that years of effort to develop new products were put on hold while FDA reviewers labored to process a flow of drug applications that greatly outpaced their capacity to manage a growing workload;

• Investments in pharmaceuticals and medical product research and development were moving to Europe and industry leaders decried the lost jobs and other economic detriments caused by the "drug lag" with Europe,

• And FDA officials proposed and developed a series of initiatives to speed the review of new drugs, none of which managed to significantly reduce drug review times.

Then, in 1992, this committee took the lead in drafting legislation to create a new program for addressing the "drug lag," and it has been, in my opinion, one of the most successful statutes ever enacted for improving public health.

THE PRESCRIPTION DRUG USER FEE ACT

The drug user fee act, known by its acronym, PDUFA, has been a remarkable success story. In rapid succession after PDUFA's creation, FDA's time to review new drugs dropped steadily; new, life-saving drugs flowed to patients more rapidly than ever before; investment in medical R&D climbed steadily, resulting in yet more new drug discoveries; and the United States seized and maintained its lead in global pharmaceutical development. Today, thanks to PDUFA, drugs are reviewed in the United States as fast as or faster than anywhere else in the world, with no diminution in FDA's historically high standards for drug safety.

In essence, Congress instructed FDA that review speed mattered, but not at the expense of safety; and mandated that FDA be given new resources to apply to drug reviews, but would be expected to manage those resources in a documented, business-like method—with program activities closely tracked and progress carefully assessed. Drug sponsors, in turn, were given more access to FDA scientists, so that they could better understand FDA's requirements and design better clinical trials, resulting in better applications that could be reviewed more easily by FDA scientists. Thanks to this remarkable program, well over a thousand new treatments have flowed expeditiously to patients since its enactment, saving countless lives and reducing untold suffering. For this reason, I join the many others who have urged you to act quickly to reauthorize the PDUFA program as negotiated between FDA and the pharmaceutical industry.

THE DOWNSIDE TO PDUFA

Despite its overwhelming success in improving the process for reviewing new drugs, I must take note of some effects flowing from the PDUFA program that are problematic. First and foremost, budget managers have allowed the infusion of new user fee funds to offset appropriations, despite efforts by Congressional drafters to utilize "triggers" to prevent that outcome. As a result, while total FDA resources and staffing have increased since PDUFA's inception, the agency's non-user fee resources have actually declined. This is best illustrated by the attached graph, which shows total FDA staffing growing, while staff paid by appropriated dollars have declined by a thousand over the past decade—an enormous decline for an agency as small as the FDA. The practical effect of this has been the loss of staff for such critical FDA programs as drug safety and protection of the food supply.

A second concern raised by PDUFA is the extent to which user fees are paying for drug review expenses. When the program was first developed fifteen years ago, it was conceived as a relatively limited supplement to the existing drug review staff, to enable FDA to deal with a large and growing drug application workload. By the end of PDUFA II, in the early years of this decade, fears arose that the percentage of the drug review program that would be paid by user fees was approaching 50 percent. FDA leaders, joined by industry, consumer, and patient groups, expressed concern that the program not pass the 50 percent point, out of fear that over-reliance on industry fees could slowly but inexorably lead to greater industry influence in FDA's decisions whether to approve or disapprove a given drug. Unfortunately, that 50 percent level was passed in PDUFA III. This has been caused by decisions to hold down or reduce FDA's annual appropriations. So, for example, in a given year the PDUFA fees are adjusted to stay even with FDA's increased costs—usually about 6 percent per year. But FDA's appropriations in recent years have been well

below its inflationary costs, meaning that the portion of the drug review program funded by fees has risen steadily. If this continues unabated, it is quite possible that the percentage of the program paid by user fees could exceed 70 percent, a level that raises both fairness questions for drug sponsors and concerns about industry influence in FDA decision-making. Therefore, I urge the committee to consider ways of "rebalancing the ledger" so that the original intent of PDUFA is restored.

THE NEXT CHALLENGE IN DRUG DEVELOPMENT

I will close with a final observation about FDA's drug program. PDUFA has been momentous for its success in improving the speed to market of new drugs. But there are two other critical legs to what one might call the drug development "tripod." The first is one the committee will likely be wrestling with this year as well—the safety of drugs once they are on the market. As new funds have flowed to FDA for the drug review program, the drug safety staff that monitors drugs on the market has not been increased, despite an ever-increasing workload. I have attached a graph that demonstrates the enormous increase in adverse event reports being submitted to FDA reports that are intended to give FDA early clues as to whether a marketed drug should be relabeled, restricted, or even withdrawn. This increase in workload has overwhelmed FDA's drug safety function, and as a result, problems with drugs such as Vioxx are likely to continue. FDA officials have ideas for substantially improving the drug safety system focused on using new technologies to capture drug safety "signals" sooner and more thoroughly. I urge you to hear their views and to assist them in gaining the appropriations to fund their solution to this vexing problem.

My last point relates to drug development time—the years, often a decade or more, from the time a new drug is synthesized in a laboratory to the time it actually starts treating patients as an approved drug. While drug review times within the FDA dropped rapidly and substantially thanks to the PDUFA program, drug development times have remained too high. Further, drug manufacturer continue to pursue "dry holes" that are expensive and shift focus away from successful therapies (the vast majority of drugs making it to the human testing phase ultimately fail). Also, the number of submissions of new drugs for approval by the FDA has flattened out, suggesting that the next wave of new drug discoveries will be harder to find and develop. Indeed, there is substantial evidence that the current "path" to new drug development is increasingly challenging, inefficient, and costly. FDA has made a proposal to decision makers that it calls "The Critical Path." It is offering to bring to bear its considerable experience in drug assessment to the development of powerful new scientific and technical methods (such as computer-based predictive models, biomarkers for safety and effectiveness, and new clinical evaluation techniques), to help drug manufacturers become more efficient and more successful in their decisions about which therapies to pursue and bring to market—with the expectation, of course, that the public will ultimately benefit by having more and better drugs made available for their treatment as rapidly as possible. But FDA has been unable to secure funding for this initiative, despite widespread expressions of support for the concept. I urge you to consider the Critical Path program an important part of your mission to improve the FDA's drug program and to impress upon your Appropriations colleagues the importance of funding that initiative.

Indeed, Mr. Chairman, an increase of just $40 million a year for five years, for a total increase in appropriations of $200 million annually by the fifth year, would, in my opinion, both "fix" drug safety and provide the necessary funding for the Critical Path initiative. I believe that such relatively modest sums would be repaid many, many times over in the development of new therapies and the successful treatment of our citizens and, as such, would be an investment of tremendous value to our society.

I again applaud the Committee for its groundbreaking work in enacting PDFUA and thereby successfully addressing a major national problem. And I thank you for letting me express my views today on its reauthorization.

Mr. PALLONE. Thank you. Sorry about the slide. I don't know, maybe we can get it passed out later. Mr. Thew.

STATEMENT OF JIM THEW, PATIENT ADVOCATE, AMYOTROPHIC LATERAL SCLEROSIS ASSOCIATION

Mr. THEW. Good afternoon, Mr. Chairman and Congressman Deal and the members of the subcommittee. My name is Jim Thew

and I am from Machesney Park, IL. I appreciate the opportunity to speak with you this afternoon on behalf of the ALS Association and the people living with ALS across the country. I was diagnosed with ALS in July 2004. At the time, I had no idea what ALS was. But when doctors say I am sorry, you don't have cancer, you know that is not good news.

ALS is better known as Lou Gehrig's disease. It is a neurological disease that destroys a person's ability to control their muscles. You can see what the disease has done to me. I can no longer stand or walk without assistance. I spend most of my time in this wheelchair. You can hear the disease in my voice. It has taken away my ability to speak. At night, I am in need of assistance of a machine called a bipap to help me breathe. That is what this disease has done to me so far, but it will continue to progress as it gets worse.

I call ALS the monster. That is because it is the scariest thing I have ever faced. I met a young man by the name of Eric Oberman from Alabama when I was in DC last year for the ALS Association's advocacy days. He was 24 years old, his whole life ahead of him, but the only thing he could move was his toes. He could not speak. He could not breathe without a ventilator. He could not even nod his head or wink his eyes. But he was alive; you could see the life within his eyes; that he knew exactly what was happening and that is why I call ALS the monster. I know that this is what ALS will do. It can strike anyone regardless of their age, gender or race. It is not discriminative. And it is fatal. Usually the average lifespan is 2 to 5 years.

What bothers me is that we don't know enough about this disease. We know it strikes military veterans like myself at about twice the rate as the general population, but we don't know why. That is why we need to have more funding for ALS research at the Department of Veterans and the VA. We know ALS is a rare disease, but we don't know how many may strike. That is why we need a national ALS registry and why I hope Congress will pass the Registry Act, which is expected to be introduced soon by Congressman Engel. Mr. Chairman, I also want to thank you for cosponsoring the bill last year and I hope you will do so again.

We also don't have an effective treatment for ALS and that is why PDUFA is so important, because we need encouragement and a speedy access to new drugs that will benefit people like myself. There is currently only one drug approved to treat ALS. However, Rilutek, which was approved in late 1995, prolongs life by just a few months and only in a few patients.

PDUFA includes a number of important provisions and goals that the ALS Association strongly supports. First, PDUFA provides needed resources to the FDA; second, PDUFA will help speed drug development and drug reviews; third, PDUFA would improve the use of technology to fight ALS; and PDUFA includes important provisions that will promote the collaboration between industry and the agency.

I hope that I have given you a better understanding of why PDUFA is so important to people like me. I also hope that you will view this from our perspective; that you recognize the urgent need to act; that you not delay passing PDUFA by adding provisions; and that issues like drug safety must not hinder access to new

treatment. It may be a matter of policy for you, but it is a matter of life and death for me. Earlier, I told you about what ALS is doing to me physically. What you don't see is the real impact of the disease. I want to watch my son graduate high school, who is only 10 years old. I want to be able to walk my daughter down the aisle on her wedding day. I want to grow old with my wife. I want to see my grandkids. To do all of that, I need a treatment for ALS. I hope that you will act quickly and reauthorize PDUFA and help me fight against this monster. Thank you for inviting me here today.

[The prepared statement of Mr. Thew follows:]

TESTIMONY OF JIM THEW

Good morning Chairman Pallone, Congressman Deal and members of the subcommittee. My name is Jim Thew and I am from Machesney Park, Illinois. I appreciate the opportunity to speak with you this morning on behalf of The ALS Association and people living with ALS across the country. I hope that by hearing my experience living with this disease, you will gain a better understanding of the needs of people with chronic and life-threatening conditions and why it is so important that Congress act swiftly to reauthorize the Prescription Drug User Fee Act.

I was diagnosed with ALS in 2004. At the time, I had no idea what ALS was. Amyotrophic lateral sclerosis meant nothing to me, as I'm sure it means nothing to thousands of others when they are first diagnosed. But when doctors say "I'm sorry, you don't have cancer," you know it's not good.

ALS is better known as Lou Gehrig's disease. It is a neurological disease that destroys a person's ability to control their muscles. You can see what the disease has done to me. I can no longer stand or walk without assistance. I spend most of my time in this wheelchair. You can hear the disease in my voice. It's taking away my ability to speak. At night, I need the assistance of a bipap machine to help me breathe. That's what the disease has done to me so far. But, it will continue to progress. It gets worse.

I call ALS "the monster." That's because it's the scariest thing I've ever faced. I met a young man from Alabama when I was in Washington last year for The ALS Association's Advocacy Day. He's 24 years-old. His whole life ahead of him. But the only thing he could move was his toes. He could not speak. He could not breathe without a ventilator. He couldn't even nod his head or wink an eyelid. But he was alive—you could see the life in his eyes. That he knew exactly what was happening. And that's why I call ALS the monster.

I know this is what ALS will do. It can strike anyone, regardless of their age, gender, or race. It does not discriminate. And it's fatal; usually in an average of two to five years.

What bothers me and why I am here today is that doctors and researchers don't know enough about this disease. We know it strikes military veterans like me at about twice the rate as the general population. But we don't know why. That's why we need more funding for ALS research at the Department of Defense and the VA. We know ALS is a rare disease. But we don't know how many it strikes. That's why we need a national ALS registry and why I hope Congress will pass the ALS Registry Act, which is expected to be introduced soon by a Member of this subcommittee, Congressman Engel. Mr. Chairman, I also want to thank you for cosponsoring the bill last year and hope you will do so again.

We also don't have an effective treatment for ALS. And that's why the Prescription Drug User Fee Act is so important because we need to encourage innovation and speed access to new drugs that will benefit people like me. There currently is only one drug on the market specifically approved to treat ALS. However, Rilutek, which was approved by the FDA in late 1995, has demonstrated only modest effects, prolonging life by just a few months and only in some patients. Unfortunately, I'm not one of them.

PDUFA includes a number of important provisions and goals that The ALS Association strongly supports.

FDA RESOURCES

First, PDUFA provides needed resources to FDA. When I learned that the FDA receives less funding than what some school districts get, I didn't believe it. As

someone whose life depends on the FDA's ability to quickly review new drugs and promote drug development, I strongly believe the FDA needs additional resources to do its job and help people like me. The ALS Association believes that the PDUFA plan put forth by the FDA will provide a much-needed increase in staff and resources and will help the Agency ensure that people have timely access to safe and effective medicines.

DRUG DEVELOPMENT AND REVIEW

Second, PDUFA will help speed drug development and drug reviews. As I mentioned, people with ALS currently have only one treatment option. And it's not a great one. However, we hold onto the hope that our Nation's scientists and researchers will develop new treatments for the disease that can slow its progression, improve quality of life and, ultimately cure and even prevent the disease from arising. That's why it is so critical that PDUFA promote drug development and expedite drug reviews and approvals, including for products not specific to ALS. After all, people with ALS can benefit from advances in the treatment of other neurological conditions such as MS, Parkinson's and Alzheimer's.

The Association supports the timelines and goals outlined in PDUFA concerning the prompt review of drugs. Delays in drug reviews mean denied access to potential life-saving therapies for people like me—to withhold a drug in order to obtain an unreasonable amount of data could cause patients to suffer or die due to the lack of access to new treatments.

ENHANCED TECHNOLOGY

Third, PDUFA would improve the use of technology at FDA. I spend a great deal of time on e-mail and on the internet. For people with ALS, information technology is our window to the world. It helps us to easily communicate and interact with others especially as the disease robs us of the ability to move and to speak. It's also how we learn about new ways to fight this disease. It's clear to me that the FDA also can use information technology to fight ALS by streamlining the drug development and drug review process. It allows the agency to rapidly collect, analyze and understand the enormous amount of information gathered throughout the lifecycle of a drug, during development and after it is approved. The ALS Association is pleased that the PDUFA plan submitted to Congress is an important step forward in using technology to find treatments and cures for diseases like ALS.

COLLABORATION

Fourth, PDUFA includes important provisions that will promote collaboration between industry and the Agency, helping to expedite drug development. This collaboration builds on efforts underway with the Critical Path Initiative. I first heard about the Critical Path Initiative when The ALS Association invited the FDA to speak at our Public Policy Conference last May. I am encouraged that the Agency is making additional efforts to help improve clinical trial design and provide other guidance that enable us to speed the development of new drugs and decrease their cost to develop. I am also encouraged that for the first time FDA has recommended that fees be used to hire additional staff that will make it easier for the agency to collaborate in the scientific research leading to new treatments and to streamline the regulatory process. What is really important to me about this plan is that it is not just focused on the drug review process. It also is designed to speed drug development. The ALS Association is pleased that PDUFA would provide full-time permanent staff and funding for this much needed collaboration that surely will benefit people with ALS and other life-threatening diseases.

I hope that I have given you a better understanding of why PDUFA is so important to people like me. I also hope that you will view this from our perspective—it may be a matter of policy for you, but it's a matter of life and death for me.

Earlier I told you about what ALS is doing to me physically - what you can see and hear in my voice. What you don't see is the real impact of the disease. I want to be able to watch my son graduate from high school. I want to be able to walk my daughter down the aisle on her wedding day. I want to grow old with my wife Kumi and play with our grandkids. To do all of that, I need a treatment for ALS. I hope you will act quickly to reauthorize PDUFA and help me in the fight against this monster. I don't have time to wait.

Thank you again for inviting me to be here today.Summary of Key Points

PDUFA includes a number of important provisions and goals:

FDA Resources. PDUFA provides needed resources to FDA. As someone whose life depends on the FDA's ability to quickly review new drugs and promote drug devel-

opment, I strongly believe the FDA needs additional resources to do its job and help people like me. The ALS Association believes that the PDUFA plan put forth by the FDA will provide a much-needed increase in staff and resources and will help the Agency ensure that people have timely access to safe and effective medicines.

Drug Development and Review. PDUFA will help speed drug development and drug reviews. People with ALS currently have only one treatment option, which prolongs life by a few months only in some patients. It is critical that PDUFA promote drug development and expedite drug reviews and approvals, including for products not specific to ALS. After all, people with ALS can benefit from advances in the treatment of other neurological conditions such as MS, Parkinson's and Alzheimer's.

The Association supports the timelines and goals outlined in PDUFA concerning the prompt review of drugs. Delays in drug reviews mean denied access to potential life-saving therapies for people like me—to withhold a drug in order to obtain an unreasonable amount of data could cause patients to suffer or die due to the lack of access to new treatments.

Enhanced Technology. PDUFA would improve the use of technology at FDA. FDA can use information technology to fight ALS by streamlining the drug development and drug review process. It allows the agency to rapidly collect, analyze and understand the enormous amount of information gathered throughout the lifecycle of a drug, during development and after it is approved. The ALS Association is pleased that the PDUFA plan submitted to Congress is an important step forward in using technology to find treatments and cures for diseases like ALS.

Collaboration. PDUFA includes important provisions that will promote collaboration between industry and the Agency, helping to expedite drug development. This collaboration builds on efforts underway with the Critical Path Initiative. The Association is encouraged that the Agency is making additional efforts to help improve clinical trial design and provide other guidance that enable us to speed the development of new drugs and decrease their cost to develop. The Association also is pleased that for the first time FDA has recommended that fees be used to hire additional staff that will make it easier for the agency to collaborate in the scientific research leading to new treatments and to streamline the regulatory process. This collaboration surely will benefit people with ALS and other life-threatening diseases.

The ALS Association encourages Congress to promptly reauthorize PDUFA this year.

Mr. PALLONE. Thank you so much, Mr. Thew, for being here today and you remind us about the need for timeliness and why we have to act quickly and I appreciate that. Thank you. Ms. Holcombe.

STATEMENT OF KAY HOLCOMBE, SENIOR POLICY ADVISOR, GENZYME CORPORATION

Ms. HOLCOMBE. Chairman Pallone, Ranking Member Deal and members of the subcommittee, thank you for the opportunity to testify today about the reauthorization of the Prescription Drug User Fee Act.

Genzyme Corporation, my company, chairs the PDUFA committee for the biotechnology industry organization and today I am speaking on behalf of BIO. Like Genzyme 25 years ago, most biotechnology healthcare companies currently are working to bring their first product to market. A strong, effective and efficient FDA is critical to these BIO members. Mr. Chairman and members of the subcommittee, my most important message to you is thank you. This subcommittee and this committee have been instrumental from day one in enacting and overseeing the PDUFA program and in ensuring its reauthorizations. PDUFA is credited with helping enhance FDA's capacity to evaluate the effectiveness and safety of new drugs and biologics, without reducing the agency's high standards or commitment to empirically-based and thorough product evaluation. But a successful program is not a perfect program and additional improvements can help address FDA's increasing work-

load and provide 21st century tools to evaluate prescription drug products pre and post-market. You have received a full description of the recommended PDUFA IV modifications from FDA and I will not repeat them. BIO supports these recommendations.

I want to focus specifically on a few things associated with the increased user fees dedicated to modernization and enhancement of FDA's post-market safety activities. The PDUFA IV recommendations, if enacted, will provide an increase of nearly $150 million over 5 years, for a variety of activities, many of which were those kinds of activities recommended in the recent report of the Institute of Medicine. For example, the new funds will allow FDA to improve its IT infrastructure for more efficient and sophisticated post-market monitoring and analysis, and to enhance the analytical skills necessary for an up-to-date post-market surveillance system based on health information technology.

FDA also will be able to utilize large medical databases to mine for potential safety signals and to evaluate them. FDA will be better equipped to identify and characterize adverse events that may not have been seen in clinical trials, to continue to assess product benefit risk profiles, in light of new data, and to provide physicians and patients with useful updated information. The additional funds also will allow the agency, with its own and outside safety experts, to evaluate post-market risk management plans to identify the most successful strategies and disseminate them.

Mr. Chairman, BIO joins FDA and others in supporting the PDUFA IV recommendations, including funding for FDA's critical path activities to help expedite drug development, continued improvements in pre-market review, including improved processes to achieve the best drug labeling, and to develop post-market studies mostly likely to provide useful information for doctors and patients, and as I mentioned briefly, to make significant post-market safety improvements.

The PDUFA IV proposals include substantial new resources for FDA. However, Mr. Chairman, FDA also needs adequate appropriations for its human drug review activities. PDUFA fees are intended to be additive to, not a substitute for a sound base of appropriations. But user fees now account for more than 50 percent of the cost of human drug review and that percentage is rising. Unless appropriations increase substantially more than they have over the last 10 years, user fees will account for more than two-thirds of the cost of human drug review activities at the FDA by the end of PDUFA IV. This imbalance of fees versus appropriations creates an unseemly misperception that FDA must be or will become beholden to the industry it regulates. This perception is not in the best interest of the FDA, it is not in the best interest of the regulated industry, and it is not in the best interest of consumers. BIO is working with the Administration and Congress to seek needed appropriations increases for FDA. We strongly urge this subcommittee to continue your activities, as well, in this regard.

In conclusion, Mr. Chairman, BIO urges timely reauthorization of this successful program. We also respectfully request and urge that the PDUFA IV reauthorization be passed unencumbered by unrelated, complex and contentious issues that could slow or jeopardize its passage and enactment. I want to thank you again, Mr.

Chairman and Ranking Member Deal, on behalf of BIO and myself, for inviting us to participate in today's hearing. It is a great honor for me, personally, to appear before you. Thank you.

[The prepared statement of Ms. Holcombe follows:]

TESTIMONY OF KAY HOLCOMBE

Chairman Pallone, Ranking Member Deal, and members of the Health Subcommittee, thank you for the opportunity to testify before you today on the success of the Prescription Drug User Fee Act (PDUFA) and the proposed enhancements for PDUFA IV.

My name is Kay Holcombe and I am Senior Policy Advisor for Genzyme Corporation. As one of the world's foremost biotechnology companies, Genzyme is dedicated to making a major positive impact on the lives of people with serious diseases. Founded in Boston in 1981, Genzyme has grown from a small start-up to a diversified enterprise with more than 9,000 employees in locations across the United States and spanning the globe. Genzyme is a leader in the effort to develop and apply the most advanced technologies in the life sciences to address a range of unmet medical needs. Over the past two decades Genzyme has introduced a number of breakthrough treatments and diagnostics in the areas of inherited disorders, kidney disease, orthopaedics, transplant and immune disease, and cancer, which have provided hope to patients who previously had no viable treatment options.

Today I represent the Biotechnology Industry Organization. BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States. BIO members are involved in the research and development of healthcare, agricultural, industrial and environmental biotechnology products. Like Genzyme at its start, most biotechnology companies are currently working to bring their first innovative product to market. A strong, credible, and efficient Food and Drug Administration (FDA) plays a critical role in enabling BIO member companies' success in creating the next generation of biotechnology medicines.

PDUFA HAS BEEN A SUCCESS

The PDUFA program has been widely credited as an innovative program that has strengthened the Food and Drug Administration's (FDA's) capacity to evaluate the safety and effectiveness of new drugs and biologics, thereby expediting the availability of needed new therapies for patients. Congress enacted PDUFA to provide FDA with additive, consistent, multi-year resources to increase its review capacity, including new medical and scientific expertise, so the agency could become more efficient without reducing its commitment to the highest standards of empirically based product evaluation. In fact, since its inception in 1992, PDUFA has helped enable FDA to approve more than 1,200 new medicines and reduced review times for innovative drugs and biologics, providing patients and doctors with earlier access to breakthrough treatments.

While the program is successful, additional improvements can help address FDA's increasing workload and provide the agency with 21st century tools to evaluate prescription drug products. The recommended PDUFA IV improvements will enhance both FDA's post-market safety capacity and review infrastructure. BIO played a role in the consideration of these proposals and fully supports these recommendations. We urge Congress to adopt this framework in reauthorizing PDUFA in a timely manner prior to its expiration.

A LIFECYCLE APPROACH TO DRUG SAFETY EVALUATION

BIO endorses the PDUFA IV proposals because they underscore our commitment to patient well-being and safety by supplementing the Agency's resources to enhance and modernize the drug safety system in the United States. Safety is an integral and paramount part of companies; considerations during research and development, FDA's deliberations during application review, and as part of post-market monitoring by the agency and by companies. When considering improvements to the Food and Drug Administration's safety evaluation system, the following principles should be taken into account.

BIO PRINCIPLES FOR CHANGES TO DRUG SAFETY EVALUATION AND MONITORING

• FDA Should Continue to Lead in Evaluating Safety and Efficacy. In the United States, the FDA is, and should remain, the government reviewer of benefits and risks of regulated products. FDA's scientific knowledge and expertise is essential for evaluation of safety and efficacy of medicinal products and FDA must have sufficient resources to complete its mission. Also, the Agency should be provided with the flexibility to distribute its resources to maximize efficiency and value. FDA's current organizational structure, which deals with drug and biologic safety pre- and post-approval in an integrated way, is appropriate for the comprehensive and systematic evaluation of safety throughout the lifecycle of medicines.

• Benefits and Risks Must be Considered Together: All drugs and biologics carry both benefits and risks that should be carefully weighed by patients and their doctors.— The balance between the benefits of treatment and the risks of potential side-effects will differ based on many factors, including the nature of the treatment and the condition, and each patient's unique medical profile. Efforts to improve safe use of medicines should support and inform medical decisions made by patients and their physicians, rather than limit the ability of physicians to prescribe a particular medicine to a particular patient. This will help to ensure that patients continue to have access to medications they and their physicians believe they need.

• Patients and Practitioners Benefit from Timely, Accurate, and Relevant Information: Patients and physicians need timely, accurate, and relevant information about the benefits and risks of a drug or biologic so they can make well-informed choices about therapy. FDA's assessment and communication of emerging information regarding a treatment's benefits and risks, both before and after approval, provides a needed integrated system of medical product evaluation. Safety information collection, communication, and regulatory action should be informed by the best available scientific data and expert advice.

• Safety Systems Should Support and Reflect Innovation: The most beneficial policies and actions with respect to drug safety are those that continue to enhance patient health and that promote innovation and the development of novel medicines. Biotechnology companies are on the leading edge of scientific advances in biomedical science and bioinformatics. The public and private sector should work collaboratively to harness and use these advancements to enhance, optimize, and modernize the system of drug and biologic safety evaluation.

BIO believes the negotiated PDUFA IV reauthorization proposals are fully consistent with these principles and should be implemented. Additionally, these principles would support the establishment of a private-public partnership to conduct routine, active surveillance through the use of population-based medical databases. Such a system could identify safety signals and analyze the findings, so meaningful information can be communicated to the public to support individual medical decisions. In addition, based on the information gleaned from such a 21st Century active surveillance program, FDA can determine what, if any, additional risk mitigation steps might be appropriate. Certain other drug safety proposals, such as a separate office of drug safety, conditional product licensure, one-size-fits-all risk management strategies for all drugs, or restrictions on a physician's ability to prescribe an appropriate treatment to a patient, would not be in accordance with these principles.

MODERNIZED APPROACHES TO POST-MARKET SURVEILLANCE

PDUFA III provided FDA with $71 million to ensure efficient risk management after a product was approved, and the PDUFA IV recommendations would build on that commitment. The PDUFA IV post-market safety enhancements would provide FDA with nearly $150 million over five years to establish a foundation of epidemiological expertise, IT infrastructure, and programmatic skill sets necessary for an up-to-date post-market surveillance system based on 21st century advances in science and health information technology. With this funding, FDA would be able to further its public health mission while continuing to enable access to safe and effective medical products. Along with modernizations to current adverse event collection systems, FDA would have the capacity to utilize large medical datasets to mine for potential safety signals actively and to subsequently facilitate the testing of those signals. With this capacity, FDA would be better equipped to identify adverse events that might not be evident in clinical trials.

Based on these recommendations, FDA would establish its vision for a 21st century drug safety system based on a five-year plan developed with the input of the public, academia, and industry experts. FDA would establish best scientific practices for conducting analyses of medical data sets, validate post-market risk management and minimization plans to identify the most successful strategies and disseminate

information about such strategies, and study how to maximize the value of adverse event reporting and analysis during a product's marketed life.

EXPEDITING DRUG DEVELOPMENT

Additionally, these PDUFA proposals would provide FDA with the resources necessary to draw on recent advances in genomics and biomedical science to develop information to help improve drug development through earlier ability to predict risks and develop appropriate ways to manage them. For example, FDA would release several guidances to expedite drug development. These guidances would outline the agency's latest thinking on how to predict certain toxicities more accurately and how to enhance the quality of the information developed through clinical trials. FDA and stakeholders would work together to develop tools necessary to further work in personalized medicine, such as new validated safety and efficacy biomarkers and new ways to measure variation in patient response.

IMPROVED PROCEDURES TO ENSURE TIMELY AND VALUABLE PRE-MARKET REVIEWS

FDA also would improve the processes for developing clear and concise product labels and scientifically appropriate post-market commitments. Often, discussions of product labeling and phase IV trials occur near the end of the review period with limited time for meaningful dialogue and few standardized procedures. The PDUFA IV recommendations include that FDA would plan for adequate time in the review process for these critical discussions, usually 30 days before the user fee date. Allotting this time for meaningful discussion will lead to enhanced safety information emerging from post-market trials and clearer label information for patients and physicians.

Reducing Medication Errors. In addition, the PDUFA IV recommendations include a program under which FDA would improve the process for review of prescription drug product names, to minimize the potential for medication errors caused by name confusion. According to the Institute of Medicine (July 2006), 1.5 million preventable medication errors occur each year in the United States and some of these mistakes are caused by confusion over the drug's name. The PDUFA IV recommendations improve the process for evaluating proprietary drug names so that concerns can be identified earlier, before a product goes on the market.

Information Technology Enhancements: PDUFA IV provides FDA with additional resources to establish an automated standards-based information technology environment for the exchange, review, and management of information supporting the process for the review of human drug applications throughout the product life cycle. These IT enhancements will lead to more efficient, higher quality evaluation of new and marketed drugs.

The PDUFA IV recommendations, in conjunction with the new safety initiatives FDA announced in response to the Institute of Medicine report (Sept. 2006), allow FDA to establish a modern, comprehensive, life-cycle approach to drug safety based on 21st century information technologies, biomedical advances, and efficient risk management strategies.

SIGNIFICANTLY ENHANCED FUNDING BASE FOR PDUFA

From its inception, the PDUFA program has been about efficient review of applications for new prescription drug products. The PDUFA IV recommendations include significant new resources—more than $50 million—to reinforce the program's financial base and ensure that the program can continue to meet its goals. These new funds allow FDA to respond to inflationary pressures, unanticipated work volume and intensity, facilities-related costs, and increased need to meet with sponsors and to review special protocol assessments (SPAs).

PDUFA Cannot Succeed Without Strong Appropriations for Human Drug Review

While we applaud the new recommendations in PDUFA IV, BIO notes that PDUFA fees are intended to be additive to a sound base of appropriations for FDA's core activities. However, BIO is concerned that FDA has become over-reliant on these user fees to meet the core mission of the human drug program. For instance, appropriations funded 150 fewer reviewers in 2005 compared to the start of the program in 1992. In 2005, fees funded more than half of the cost of human drug review, compared to 7% at the start of the program. Unless appropriations increase substantially more than they have over the last 10 years, user fees could account for more than two-thirds of the cost of human drug review by the end of PDUFA IV. BIO is concerned that FDA's over-reliance on industry fees creates an unseemly misperception that FDA is beholden to the industry it regulates. In the long-term, this perception is not in the best interest of patients, biopharmaceutical innovators

or FDA. The fee increases proposed under PDUFA IV are necessary for FDA to implement the new proposals which will enable them to continue to make needed new medicines available to patients, but BIO believes that FDA also needs increased appropriations to continue its mission of protecting patients as it faces a revolutionary new era of scientific innovation and advancement.

BIO is a founding member of the Coalition for a Stronger FDA, a group of trade associations, patient groups, consumer advocates, and individual companies whose goal is to ensure a strong, consistent public commitment to resources for the FDA. In addition to user fees, it is important that FDA receive a reasonable balance of appropriations for human drug review. BIO and the Coalition for a Stronger FDA will continue to work with the Administration and Congress to seek needed increases in appropriations for human drug review activities at FDA over the next five years.

PDUFA SHOULD BE REAUTHORIZED IN A TIMELY MANNER

It is important that Congress complete this reauthorization in a timely manner to avoid program interruptions, the initiation of a reduction in the FDA workforce, and slow-down in regulatory reviews that will reduce patient access to new therapies. PDUFA should not be slowed or unencumbered by unrelated or scientifically contentious issues. BIO looks forward to working with members of the committee to ensure that this PDUFA package is reauthorized expeditiously and well in advance of the statutory expiration of PDUFA III on September 30th 2007.

In conclusion, BIO believes that the PDUFA program has been highly successful and is a direct contributor to increased patient access to life-saving, breakthrough therapies. The proposed enhancements for PDUFA IV would provide FDA with tools and resources to modernize the post-market surveillance system, evaluate more efficiently each product's unique benefits and risks, and continue to support the timely development and availability of new medicines to patients.

Thank you and I would be happy to answer any question from the committee.

Mr. PALLONE. Thanks so much. Mr. Vaughan.

STATEMENT OF WILLIAM VAUGHAN, SENIOR POLICY ADVOCATE, CONSUMERS UNION

Mr. VAUGHAN. Thank you all for inviting Consumers Union, the publishers of Consumer Reports, to testify today, and I guess I will have a little bit different tone but similar outcome on all of this. We think there is a lot of wisdom in the old saying, who pays the piper calls the tune, and that is why we oppose funding a vital consumer protection agency out of industry user fees that are essentially really a tax on people who take medicines. It would be far, far better if the entire FDA budget were funded by the progressive tax system. The user fee system is damaging to the image of the FDA, as Kay just indicated, and morale of the staff and to the public because it compromises drug safety.

On the image issue, Consumers Union has just conducted a national poll. It found the public overwhelmingly wants stronger drug safety protections, but 84 percent feel the industry has too much influence over the regulators, with two-thirds concerned about the user fee system. And on morale, Representative Baldwin cited the Union of Concerned Scientists survey. I put some of those quotes in my written testimony, which I ask permission to be put in the record, please, and I hope you could look at them because they are truly frightening. And recently, as Representative Capps noted, four former FDA commissioners spoke in favor of appropriations over user fees. So our dream is to see the FDA totally funded out of appropriations. Well, as you said, Mr. Chairman, it isn't going to happen, not in this budget climate and these tough budget days. But we hope that you might work for this in the long run, because

it really would be helpful. Or achieve the same purposes of improved image and morale and drug safety by keeping the user fees but breaking the strings that the industry has put on the agency. Those strings were the main concern about users fees in the Institute of Medicine's report. We urge you to consider Representatives Hinchey and Stupak's bill of the 109th that would keep user fees but break the strings. Whatever happens, whatever happens, it is vital that Congress give the agency more resources, as Mr. Hubbard has said, and greater authority to conduct post-market approval safety activities. We do not want to take resources away from or in any way slow down the approval of possibly lifesaving drugs. We so strongly agree with the ALS witness on that. As we see it, nothing in the FDA reform bills, Grassley-Dodd, Enzi-Kennedy, or Waxman-Markey slows down the approval of new lifesaving drugs. But the agency desperately needs more resources and authority to match the high speed of approvals with a high speed, post-approval system that makes sure the drugs on the market really are safe and effective.

PDUFA calls for a safety increase of $29 million. That is a start but woefully inadequate. Therefore we congratulate Senators Kennedy and Enzi, who are marking up a bill tomorrow that increases PDUFA safety fees by $50 million per year above the $29 million that has been talked about, dedicating the money to their new safety initiatives and particularly to an exciting new proposal to use huge medical databases, such as Medicare's, to do epidemiological studies to detect safety programs. Congressman Deal, I think that Senate bill really takes a big step forward towards the IT problems you were talking about.

And the other issues. We urge you to look hard at the proposed voluntary advertisement user fee proposal. I am not sure it works. You should legislate that the companies get more than a slap on the wrist for bad ads so they will want to pay a user fee for preclearance. And then another issue. Since PDUFA triggers general Treasury appropriations and now involves safety, when you consider PDUFA V in 2012, and I hope you are all here, patients should get to participate in the real negotiations. Today, consumers are consulted while the others, several others at the table here, get to do the actual negotiating and I feel we are sort of at the kid's table. I would trade 10 hours of consulting for 1 hour of negotiating any day and I think you would get some better public policy out of it.

And finally, it is absolutely essential that safety legislation, like Waxman-Markey's H.R. 1561, which we strongly endorse and we hope you will all cosponsor, be included in whatever PDUFA legislation you enact. If FDA reforms that could save us from future Vioxxes are not included in that must-pass PDUFA package, we will miss the best chance in 5 years to protect the American public. Thank you very much.

[The prepared statement of Mr. Vaughan follows:]

Statement of William Vaughan
Senior Policy Analyst for Health at
Consumers Union, the independent, non-profit publisher of Consumer Reports

before the
U.S. House of Representatives'
Subcommittee on Health
Committee on Energy and Commerce
April 17, 2007

Prescription Drug User Fee Act legislation

Mr. Chairman, Members of the Committee:

Thank you very much for inviting Consumers Union[1], the independent, non-profit publisher of Consumer Reports, to testify on PDUFA legislation.

Why PDUFA is Bad Policy: The Long-Term Goal Should be General Treasury Funding

Who pays the piper, calls the tune.

We think there is great wisdom in that old folk saying, and that's why we oppose funding a vital consumer protection agency like the FDA out of industry-funded user fees. The FDA oversees the safety of about one-fifth of the U.S. economy. Its work in drugs, medical devices, and food is of life-and-death importance to each of us—and as we've just seen, to our pets. If there were ever a public function that should be funded out of the Treasury, this is it.

Instead, over half the FDA drug budget is funded by the industry it regulates. And those funds are essentially a tax on people who need to take medications, since fees are passed on substantially to consumers. It would be far, far better if the entire FDA budget were funded by the progressive tax system.

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

Impact on Image, Morale, and Culture of FDA: The user fee system—with its incredibly detailed requirements from the pharmaceutical industry for the FDA to respond to requests from industry, to schedule meetings within X weeks of a request, etc., etc., etc.—is terribly damaging to the image, morale and public service culture of the FDA.

In late March, Consumers Reports National Research Center conducted a national poll that found the American public overwhelmingly wants stronger prescription drug safety protections. The survey found that 84 percent of consumers agree that drug companies have too much influence over the government officials who regulate them. Two-thirds (67 percent) are concerned that much of the FDA's funding comes from the pharmaceutical industry, with more than half—54 percent—'very concerned' about the funding source.

A recent Union of Concerned Scientists survey found extensive FDA staff concern about the impact of PDUFA. Last year the UCS polled 5,918 FDA scientist/physicians with a 38 question survey, and received 997 responses (17 percent), with 503 providing some narrative commentary. The survey showed an agency with serious morale problems, and a frequent theme in the narratives was that PDUFA was placing pressures on employees to approve, too quickly, drugs that had unresolved safety issues. Following are typical staff comments for improving the FDA:

> "Most important: Get rid of PDUFA and increase Federal base budget. Currently, we are dependant upon user fees and this is a huge conflict of interest. 'The fox is guarding the henhouse.'"
>
> "Less emphasis on adhering to PDUFA timelines and more emphasis on quality of reviews for reviewers."
>
> "Ending PDUFA funding for review work and the reduced & restrictive time lines."
>
> "Eliminating the User Fee arrangement. It is inherently impossible to regulate industry in an unbiased manner when they are paying our salaries and expenses."
>
> "Allowing the centers to do a thorough investigation of new drug applications. In my opinion, FDA scientists are pressured to approve new drugs in a short period of time, which in turn leads to adverse reactions."
>
> "…management is heavily influenced by industry. When I go to meetings with my upper management, I honestly prepare myself as though I were going to a meeting with an industry representative."

Finally, on its face, the current system is not good government. Imagine what the public would say if Microsoft funded more than half the budget of the Department of Justice's

Anti-trust Division or Boeing paid more than half the cost of the National Transportation Safety Board. The same perception problem exists with PhRMA funding of the FDA.

Budget Reality: Eliminate Distorting Performance Standards

Having said all this, the Federal budget situation—and the constraints of the Budget Resolution now in Conference—almost certainly require us to depend on user fees for at least another year, if the FDA is to be able to continue approving new drugs.

Therefore in lieu of public funding, the next best thing would be enacting legislation like HR 2090, sponsored in the 109th Congress by Rep. Maurice Hinchey. In addition to FDA post-market safety reforms, this bill put the amount of money raised by the user fees into the general Treasury, then transferred the same amount from the Treasury to the FDA, while repealing the tight performance goals that so control FDA operations. As last year's Institute of Medicine report stated about PDUFA and FDA funding:

> "The [IOM] committee is not concerned about the existence of performance goals in principle, but finds the limitations or 'strings' that direct how CDER can use PDUFA funds the most troubling aspect of the arrangement."

Removing these distorting performance goals is particularly important in light of concerns from a February 2007 study by Harvard Professor Daniel Carpenter and others entitled, "Deadline Effects in Regulatory Drug Review: A Methodological and Empirical Analysis." The analysts found that

> The rate at which drugs experience most-marketing regulatory events is appreciably higher for drugs approved in the months before the PDUFA clock deadlines, compared to other drugs, especially those approved in the months just following the elapsing of the deadline. For non-priority molecules, pre-deadline approvals are associated with three to five times the rate of safety-based withdrawal from the global market and Canadian markets. Pre-deadline approvals have two to three times …labeling changes per year of marketing and, for drugs approved since FDAMA, over five times the rate of product discontinuations per year.

The Need for More Drug Safety Resources, including, Reluctantly, from User Fees

Ultimately, if legislation that breaks the ties and requirements that come with user fees is not possible, then we urge that post-market approval safety be given increased resources.

We do not want to take resources away from or in any way slow down the approval of possibly life-saving drugs. We see nothing in the various FDA reform bills—Grassley-Dodd, Enzi-Kennedy, or Waxman-Markey—that slows the approval of life-saving drugs. These bills do, however, give the FDA effective authority to ensure safety once such drugs come to market.

We are pleased that the final FY 2007 Congressional action singled out the FDA for increased appropriations, and that the President's budget request for FY 2008 also provides a noticeable increase for the agency, especially when compared to many other HHS agencies. But the amounts provided and requested do not make up for years of resource erosion, nor do they allow the FDA to do the job that a "gold standard" agency should be doing. More resources are needed, if not through the ideal of appropriations, then through increased user fees that give new emphasis to post-approval safety. As last September's Institute of Medicine report said,

> Regardless of the source of the funds, the committee reiterates that the functioning of a drug safety system that assesses a drug's risks and benefits throughout its lifecycle is too important a public health need to continue to be under funded.

Under PDUFA, we have become one of the world's quickest approvers of new drug applications. Consumers Union supports rapidly bringing life-saving medicines to market. But now that we lead the world in rapid drug approvals, we also face a 'safety gap' in which Americans are at times being used as, if you will, "guinea pigs" for new, mass marketed medicines. We would like to see the same emphasis given to closing the safety gap as has been dedicated to closing the 1980's drug approval gap. We need to match the high speed of approvals with a high-speed, high-quality post-approval safety system.

The PDUFA IV agreement calls for an increase in safety issues of about $29 million, and the proposal thankfully removes the limit on the period of time that PDUFA funds can be used for safety work on a particular drug. That's a start—but woefully inadequate. The IOM report called for far more than $100 million (see discussion in its Chapter 7) in new safety and scientific resources.

Support Senate bill's increase in PDUFA safety money

Therefore, while we are working for further strengthening amendments, we congratulate Senators Kennedy and Enzi for the bill being marked-up tomorrow in the Senate HELP Committee, S. 1082. We believe—*though this needs confirmation*[2]—that this bill increases the PDUFA user fees dedicated to post-market approval safety by as much as $70 million while ensuring that general appropriations will not be reduced. Further it dedicates that money

(1) to the implementation of the Enzi-Kennedy Risk Evaluation and Mitigation Strategies (REMS) and

(2) to an exciting new proposal to use huge medical databases—such as the Medicare data base—to conduct epidemiological studies to detect short and long-term safety problems.

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[2] There may be a typo in the version we have; we assume the intent is to ensure that user fees for safety do not replace appropriations (as is the intent and the law with the pre-approval user fees).

It is worth elaborating on the database monitoring proposal. It is basically from a bill by Senators Gregg, Burr, and Coburn, S. 1024. I believe that bill comes in part from an idea by former FDA Commissioner and CMS Administrator Mark McClellan, MD, that we have long supported as an addition, not a substitute to a strong FDA reform bill. Let me repeat that—this proposal must be an addition, not a substitute to stronger authorities to enforce label changes, ensure the actual delivery of promised safety studies and trials, etc. Without giving the FDA new authority to enforce safety measures when problems are discovered in the post-market arena, increased database surveillance will mean nothing. As Dr. McClellan testified before the Senate HELP Committee on March 14, 2007:

> "...according to calculations by Richard Platt [Principal Investigator of the HMO Research Network CERT]...electronic and other data actually used to determine a significant association between Vioxx use and serious cardiovascular events took almost three years to detect a statistically significant association, based on the limited population data available for analysis at the time. If data from large health plans could have been pooled to provide more definitive evidence on this potential safety risk, as envisioned by this strategy [the language in S. 1082 and S. 1024], the significant association could potentially have been detected within just several months...."

House Should Provide Even More Specific Safety Resources

We believe additional, specific safety initiatives should be funded, ideally by increased appropriations, but if necessary, by further increases in user fees. Congress should spell out some specific, hard deliverables in the safety area under PDUFA. When you look at the user fees that go to pre-approvals and speeding approval, they are used to achieve very detailed, date specific deliverables. Yet we don't get the same treatment on the safety side. The entire tone and structure of the FDA's PDUFA safety provisions as presented to the Congress and the public are different. They are, frankly, very fuzzy, very academic, and very bland.

In general, the industry gets 90 percent of new drug applications decided within a certain number of days, and requests for meetings answered within two weeks.

What does the consumer public get? In the FDA five year PDUFA IV plan, we get sentences like

> "...FDA would use these funds to continue to enhance and improve communication and coordination between pre- and postmarket review staff."

Or

> "Potential activities in this area might include integration of certain proposed recommendations made by the [IOM]."

We get

> "a public workshop to identify best practices in this emerging field, ultimately developing a document that addresses epidemiology best practices…"

As someone once said, 'where's the beef?'

Safety Deliverables

As consumers, we would like to see some tough deliverables, just like PhRMA gets. The meetings and better communication described in the agreement may be necessary, but we need more resources for specific, "on-the-street" safety work. The following list is just illustrative of the kind of safety issues we hope this Subcommittee will consider, and assumes that legislation similar to HR 1561, the Waxman-Markey bill, is enacted.

> --investigate all serious adverse event reports within 15 days, and conduct at least **XX** investigations per year into patterns or clusters of adverse event reports to determine if REMS[3] action should be taken;
>
> --make the adverse event reporting system more effective by considering pharmacist counseling and outreach programs or monitoring of AERs through personal health records;
>
> --increase by 100 percent (that is, double) the percent of clinical trial data and Investigational Review Board applications audited to ensure the ethical treatment of enrollees, the experiments' integrity, and the sponsor's compliance with good scientific practice[4]. As one witness testified before this Committee on February 13th, the IRB process is 'broken' and patients are subject to needlessly dangerous, unscientific proposals. As for the quality of Randomized Clinical Trial data, how many more Keteks are 'out there;'
>
> --each year, identify **X** of the most commonly used off-label drugs and require a Phase IV trial to determine whether there is scientific basis to support the safe and effective use of those drugs for that off-label purpose. This proposal would in no way interfere with a physician's right to prescribe or deny drugs to patients, but it would institutionalize a way of bringing some science to this area of pharmacology. A recent report estimated that 21 percent of 160 commonly prescribed drugs are prescribed off-label, and in 73 percent of the cases, there was little or no scientific support;

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[3] Risk Evaluation and Mitigation Strategies, a term used in S. 484 and S. 1082, bills by Senators Kenney and Enzi. The same framework is used in Waxman-Markey HR 1561.

[44] It is reported that the FDA is revising regulations allowing drugs used in a Phase 1 trial to be exempt from quality control manufacturing requirements. If this is accurate, there should be some system of sampling a certain percentage of these drugs for purity and safety. See Triangle Business Journal, Nov. 3, 2006, "Triangle scientists reticent about FDA shift." Additional resources in this sector will be especially needed because of the growth in trials overseas. ("Up to Two-Thirds of Clinical Trials May be Done Abroad, Study Says," Washington Drug Letter, January 8, 2007, p. 8.

--speed up the date from FY 2010 that a more diverse and 'richer' clinical trial population is used in the testing of new drugs. The current system of testing largely on healthier, middle age Caucasians masks a world of future adverse events and problems;

--increase by 100 percent the inspection of manufacturing (including compounding) facilities for compliance with FDCA laws;

--through active outreach and recruitment, develop and maintain a list of potential advisory committee specific experts who have no conflicts of interest and who have indicated a willingness to be appointed to future relevant advisory committee vacancies;

--assuming the FDA is given the legal authority, in addition to the clinical trial registry and results databases established by S. 1082 and HR 1561 for drug applications received after the enactment of this Act, develop over a phased-in four-year period ending in 2012 a similar registry of clinical trials and clinical trial results for those trials initiated or completed after 1997 and before the effective date of this Act.

--address the unapproved drugs problem. Currently about 2 percent of all prescriptions are 'unapproved' drugs, drugs which generally were on the market before 1962 and have not had to prove efficacy, or in some cases of drugs approved before 1938, have not even proved safety. The FDA has indicated that budget restraints prevent them from moving faster to determine the safety and efficacy of these drugs.[5]

Generics and Biogenerics

We appreciate the budget effort to reduce the backlog of generic drugs. We hope that the budget and, if necessary, the PDUFA agreement, will be able to assist in the implementation of legislation such as the Waxman-Schumer biogenerics legislation, once legislation like that is enacted. Biogeneric approval may be more resource intensive than traditional generic pharmaceuticals, and we will need more resources to make the promise of lower cost biogenerics a reality.

DTC User Fees: Will They Work Unless Congress Gives the FDA Civil Monetary Penalty Authority?

[5] See letter to Rep. Markey from the FDA, described in Inside Health Policy, January 9, 2007, "Markey Eyes Bill On Stronger Unapproved Drugs Enforcement."

We support pre-review of television and, frankly, all other advertisements for prescription drugs. Consumers Union's past investigations have found that companies repeatedly violate advertising standards, complete ad cycles before the FDA catches up with them, and escape without effective penalty for misleading the American public. For example, in our February 2003 Consumer Reports magazine, we noted that Claritin had received a total of 11 regulatory letters about problems with their ads. The FDA needs stronger authority in this area to stop the white lies and fibs that are found in so many ads.

We urge you to look very hard at the proposed voluntary DTC user fee proposal. We are not sure it works. If companies only get a slap on the wrist or receive a letter saying 'please stop running an ad' months and months after it has been off the air, why would they want to pay a user fee for pre-clearance? Perhaps the best way to clean up the advertising honesty mess would be to make it very clear legislatively that Civil Monetary Penalties will apply against ads that are deceptive and misleading—and that repeat violations are doubly or triply punished. That would ensure that companies submit ads for pre-review and pay the user fees necessary to support this new program.

Also, we are concerned that there are many other advertising formats—the Internet, continuing medical education forums, magazines, and pamphlets to doctors—where the adequacy and honesty of the information being provided should be audited. Clearly, in many ways, the companies repeatedly violate the rules against off-label promotion. The FDA needs to monitor more of those advertising modes—for which it will need additional resources.

Also, the definition of DTC advertisement in the draft PDUFA bill is an ad of less than 2 minutes. That would exclude from user fees the recent controversial infomercial on Celebrex, for which the company has been criticized for misleading comparisons. There is no reason to exempt any ad from the requirement of truthfulness and the 2 minute language should be adjusted.

PDUFA V: Patients and Consumers Should be at the Negotiating Table

We hope that you will include language requiring that when we consider PDUFA V in 2012, that consumers and patients get to participate in the real negotiations. Since PDUFA triggers taxpayer appropriations, and since some of the money is now being spent on consumer patient safety issues, that part of the public should be at the negotiating table, rather than just the current closed-door negotiations between PhRMA and the FDA.

Safety Legislation, like Waxman-Markey, must be part of the PDUFA package

Finally, it is absolutely essential that FDA drug safety reform legislation, like Waxman-Markey's HR 1561—which we strongly endorse and hope you all will co-sponsor-- be included in whatever PDUFA legislation you enact this year. Given this year's Federal budget situation, PDUFA is needed, must-pass legislation. If FDA reform legislation that

would save us from future Vioxx's and other drug disasters is not included in that must-pass package, we will miss the best chance in 5 years to protect the American public from unsafe drugs.

While we support the Enzi-Kennedy bill, we've been working for improvements to that bill. Many of those improvements are contained in the Waxman-Markey bill and we hope those improvements will be part of the final bill sent to the President. The Senate is joining PDUFA with Enzi-Kennedy FDA reforms. To go to Conference without a package of PDUFA and FDA reforms would put the House at a disadvantage, reduce your opportunities to participate in the safety debate, and eliminate chances to improve on the Enzi-Kennedy package.

Please don't let this once-in-a-five year opportunity to reform the FDA slip away.

Mr. PALLONE. Thank you all for your opening statements and now we will start with questions and I will yield myself 5 minutes. I wanted to start with Mr. Vaughan. A number of the committee members talked about Vioxx and you, in your written statement, use Vioxx as sort of the poster child, I guess, if you will. I wanted to use that by reference and ask you this question. You heard the testimony today. We are concerned about the timeliness of passing PDUFA reauthorization. But on the other hand, the issue is out there about whether to add drug safety or even throw in biologics or whatever. And of course the concern is, how far can we go with this and not jeopardize the timeliness of the reauthorization? You were using Vioxx as sort of an example about—I think you used it in two respects. One, you said that if you have better data collection or larger data collection, that was certainly an answer. You mentioned Mr. Waxman's bill, as well, in this context. So just give me a comment on what you think led to the Vioxx situation and what, if any, were the failings of the FDA by reference to this? I know we could talk all day, but if you could kind of summarize.

Mr. VAUGHAN. Basically not having enough information out there on the clinical trials that were done on that drug, so that it was hard for the world's researchers to really say there is a problem here, but a lot of people saw some warning signs. The VA didn't use Vioxx much. Kaiser didn't. Several State Medicaid programs avoided it. Then when there were some studies that caused the FDA to say, "hey, let us redo the label" they had to negotiate with the company for 14 months. They couldn't say, "excuse us, it is very clear to us, we want a label change tomorrow morning and by the way, you ought to cool the advertising." They couldn't do that. The legal authorities weren't there. Dr. McClellan has testified on the idea of monitoring large epidemiological databases, that the Vioxx problem probably could have been picked up in about 3 months instead of the 3 to 4 years that it took for a general consensus that, hey, this drug is trouble. To add that to PDUFA, like Kennedy-Enzi is doing could save, in a future case, thousands of lives, millions of dollars, free up research for other stuff instead of law cases. So we hope that you will expand on PDUFA and include some of these safety ideas.

Mr. PALLONE. I appreciate that. And then my second question, which I guess can be for Ms. Holcombe or Dr. Goldhammer. With regard to the direct-to-consumer advertising and we heard the testimony from the FDA representative about—that this would continue to be a voluntary system. There have been proposals for moratoriums. Of course, I worry about the constitutionality of a moratorium because of commercial speech. Are there ways of having a system that has some kind of better controls without having a moratorium? In other words, not just relying on a voluntary system because of the concern that the bad actors may not participate? But without going to 2- or 3-year moratorium which I guess I would be concerned might be thrown out by the courts on the free speech grounds, is there something in between that could be done?

Mr. GOLDHAMMER. Well, unfortunately, I am not a lawyer and can't opine on the constitutionality.

Mr. PALLONE. Yes. I am not asking you to do that. I am just asking practically.

Mr. GOLDHAMMER. There is a "but". But I will say that, since the principles were adopted by the PhRMA board a couple of years ago, we have seen a marked difference in enforcement. I think our statistics from 2006 pointed out, at least in the first 9 months, there were zero enforcement actions taken by FDA against broadcast advertisements, whereas the previous year there were 17. So we have seen a marked shift in the way the ads are submitted to FDA. They are taking that very seriously. So it may very well be that the voluntary action of industry has largely solved the problem out there.

Mr. PALLONE. I am questioning that and I am asking if there is any kind of limits on advertising other than a moratorium, that could be put in place. And I am not trying to stop you, but I am going beyond the voluntary. Maybe Ms. Holcombe or Mr. Vaughan would respond to that.

Mr. VAUGHAN. I would strongly, strongly urge pre-clearance. This is an example of talk of the pharmaceuticals. Last fall, in a back-to-school campaign, pushing sleeping pills on little kids last September. They ran the ad for a few days in September. The FDA sends them a letter in March saying, gee, please don't run that ad anymore, because this drug has no proof that it works in kids and it is probably harmful to little kids. And in March, they send the letter, nothing else. No penalty, no requirement to run ads to correct the impression that parents should pump their kids full of sleeping pills. We have got to have a better system. This voluntary system doesn't work. I assume they are not members of your PhRMA.

Mr. PALLONE. When you talk about pre-clearance, how do you do that and move away from the voluntary system?

Mr. VAUGHAN. You submit all ads and they are pre-cleared by FDA staff who reviews them for accuracy and honesty, that we are not pumping poison, if you will, into our Nation's children. Or, if you don't want to do that, how about this? Civil monetary penalties are in Waxman-Markey. Make it very clear that if you are out there with a misleading ad that doesn't list side effects, doesn't give warnings, then you pay a CMP and if you do it twice, you pay a fortune. Clariton got cited 11 times. How can people who are so smart to make a pill like that, not get the ads right?

Mr. PALLONE. OK.

Mr. VAUGHAN. I mean, this is crazy.

Mr. PALLONE. I thank you. I know my time has run out. I yield to Mr. Deal.

Mr. DEAL. Thank you, Mr. Chairman, and I want to thank all of you for being here today and Mr. Thew, especially for your efforts to be here and to testify. You certainly underscore the importance of getting drugs on the market and research that is necessary and hopefully speeding the process up for lifesaving drugs that would be important to you and to many other people.

While we are talking about the advertising, I have had a problem for a long time, understanding the reason why we would advertise something that requires a prescription to obtain. But that, nevertheless, I have been told does pay dividends, apparently, for those who choose to go that route. Mr. Goldhammer, I believe you said in your testimony that, in 2005, your association issued voluntary

standards that would say that every member of PhRMA would submit their ads for pre-approval. Can you tell us to what degree that guideline has been successful?

Mr. GOLDHAMMER. We will have to get back to you in writing. I believe that most, if not all, of the members of PhRMA have signed on to those principles, but I am not the one who is in charge of that program, but we will be happy to go back and get the exact percentage to you.

Mr. DEAL. One of the concerns that I have heard expressed, and I think the reason for the add-on to provide funding for reviewing the ads, is the delay time in getting approval under the current system and this would generate revenue that hopefully would provide personnel to be able to give a quicker approval for ads. Is that everybody's general understanding as the motivation?

Mr. GOLDHAMMER. Yes, that is correct. While we were negotiating, we got extensive statistics from the FDA about how long it was taking them to review the ads and render an advisory opinion and we have seen just, I think, over the last 3 years it has gone from about 35 days to over 80 days. And that represents a real disincentive, I believe, for companies to submit an ad for getting this advisory opinion back, if they are going to be sitting in a queue waiting and waiting and waiting for that opinion. On the other hand, companies want to get these opinions. To run a broadcast ad is not an insignificant amount of money to go through and do that and I think companies want to get it right before the ads actually air on television.

Mr. DEAL. I think all of us are concerned about this ongoing balance or mix, if you will, between industry-funded testing and certification versus Federal general taxpayer revenue, and several of you touched on that from a variety of points of view. Mr. Vaughan, I am a little interested in your survey that showed that 67 percent of Americans are concerned that funding comes from the industry. My first reaction to that is that I am surprised that 67 percent of the public even knows that fact. I presume that is because you have informed them in a previous question, is that right?

Mr. VAUGHAN. No. Of course the question asks, if drugs are approved and if partly paid by—yes, of course, sir.

Mr. DEAL. Yes. OK.

Mr. VAUGHAN. But it was a good poll. About thousand folks.

Mr. DEAL. One of the concerns that you expressed, Mr. Vaughan, was that you felt that PDUFA has compromised the safety component and you quote in your written testimony. I presume these are researchers or people employed within FDA, expressing their concerns and you have categorized them in a variety of ways. I presume that the safety issue relates to the feeling of being under a time limitation to get the work done. Is that generally it?

Mr. VAUGHAN. Yes, sir, that seems to be it. I have not worked at the FDA, but also in the testimony, there is this Harvard Professor Carpenter, who, I believe, the chairman referred to earlier, that actually tried a very sophisticated mathematical analysis and I couldn't attest to his math, but basically, things approved just before the PDUFA due date have a lot of trouble afterwards, like four or five times as many adverse events and label changes. Whereas, when the FDA takes a little bit longer and it slips a bit past the

PDUFA due date, the drugs seem to be safer or don't have as many troubles on the market. Now, we wouldn't want to slow up lifesaving drugs. If we have the cure for ALS or we think we do. For gosh sakes, bring it to market. But for the 20th kind of statin or the 40th kind of antihistamine, what is the rush that it has to be on the 10th month?

Mr. DEAL. Well, my comment to that is that FDA is a bureaucracy like many. Deadlines and time limits have good effects many times, because they don't just let you bury something within the system, but I think we all acknowledge that it is a very delicate balancing act that we have try to achieve. And my time has expired. Thank you, Mr. Chairman.

Mr. PALLONE. Mr. Waxman.

Mr. WAXMAN. Thank you very much, Mr. Chairman. Balancing is something we have to do in this legislation. In one area, of balancing, is the amount of revenues that goes into drug approval that is paid for by the user fees as opposed to appropriations. One of the things we insisted on when we adopted PDUFA is that the user fees not replace the appropriations. Rather than improving our system, we would end up in worse shape and I am just alarmed to learn about the prediction that the percentage of user fees could exceed 70 percent if we don't act to stop this ever-increasing reliance on user fees. Mr. Hubbard, what is your view of the optimal balance? What percentage of FDA's drug review funding should come from user fees as opposed to Federal dollars? And what impact has this perception had, that FDA is in the pocket of the pharmaceutical industry had on the agency and its culture?

Mr. HUBBARD. I recall that, in the late 1990's, when the percentage approached 50, then Commissioner Jane Haney and the industry folks and the consumer patient groups all felt it should not pass 50 percent. And Dr. Haney put in a large budget for appropriations that year to prevent that and to increase the appropriated dollars. However, it never came and subsequent commissioners have done that as well. So it has clearly been an effort at the FDA to try to say let us hold it down, but that has not been done. The perception certainly is that as those percentages go up to 60, 70, perhaps even 80 percent someday, that industry could be into FDA saying to the scientists, we are paying your salaries and we need our approval, and that would not be a good thing to happen. So I would urge you to do whatever you can do to increase FDA appropriations so that the percentage will stay where it is or even go down.

Mr. WAXMAN. Another imbalance, as I see, is that the amount of the PDUFA funds that will go for FDA's review of the drug compared to its drug safety program. So while PDUFA dollars are flowing freely to the drug review program, and that is increasing the speed with which new drugs enter the market, which is something we all find desirable, FDA's post-market drug safety system appears to be starving. Can you talk more about how this has occurred and the impact it has had?

Mr. HUBBARD. Absolutely, Mr. Waxman. That has undeniably happened. The post-market system at FDA has not been strengthened in the way the pre-market system has, so the imbalance has grown and grown and grown. And this gets somewhat, I think, to

Mr. Stupak's point. I will show you this chart we tried to show earlier.

[Chart shown.]

This is the increase in adverse drug reports that come to the agency. As you can see, they have increased exponentially. There were 30 people to review them in 1990 when there were 200,000, or 20,000. There are 30 people now to review them and they are 200,000.

Mr. WAXMAN. Do you think that the proposal that the FDA has presented to us that they negotiated with the industry is a good balance in this regard?

Mr. HUBBARD. Well, certainly, I very much support the negotiation that occurred, but the catch-up needs to be, in my view, on the appropriations side. I think the fact that the industry is paying more now for post-market surveillance is a good thing, but in the end, you need to have the appropriations catch up, I believe.

Mr. WAXMAN. Dr. Goldhammer, I noted that you support the limited funding for FDA to conduct certain post-market drug safety activities, as set forth in the industry/FDA proposal. I am sure you are aware of the Institute of Medicine in its very well-regarded report says that far more is needed to give Americans confidence that marketed drugs are safe. They recommend a number of significant reforms that would give FDA several new authorities, including, for example, the ability to require that post-market studies, safety studies, be conducted, to require labeling changes and to place moratoriums on DTC ads for new drugs if it is going to increase sales at a time they are not sure about the safety of it. Many of these recommendations are in the Kennedy-Enzi bill and the Waxman-Markey bill. What is your position or your view on these recommendations?

Mr. GOLDHAMMER. We were empowered during the PDUFA discussions to only focus on what could be done through PDUFA and the recognition was, when the IOM report came out in mid September, we needed to take a hard look and see, did we address what we could have addressed through the PDUFA process? And I think what FDA said and what we have said in our statement is the answer to that is yes. In terms of what could be done through more resources, we have done that. The rest of the IOM report and I think the major things, as you have noted, are, I think, issues that IOM has thrown back to Congress for——

Mr. WAXMAN. Well, what is the position of PhRMA, let us say, on the issue of whether FDA should be able to require a post-market review by the company rather than simply requesting?

Mr. GOLDHAMMER. Well, we don't have a position on any of——

Mr. WAXMAN. Well, what is your best professional judgment on that point?

Mr. GOLDHAMMER. On?

Mr. WAXMAN. On requiring the studies to be conducted post-market rather than simply requesting it and then finding it is not done.

Mr. GOLDHAMMER. Well, as we have looked at the statistics that FDA publishes on a yearly basis, only 3 percent are delayed. The vast majority of them are proceeding according to schedule. Now, I think there is a misperception in that regard, because people look

at this large number of pending studies and believe the pending studies are not on schedule, but that is not, in fact, what the FDA regulation says. If a study is pending, it means it is not delayed.

Mr. WAXMAN. There is no end date set for them. Don't you think the FDA ought to have the authority to require it?

Mr. GOLDHAMMER. Well, I think, certainly for subpart H, drugs approved under subpart H, they do have that authority today. There are end dates in almost all of the post-market——

Mr. WAXMAN. So your answer is no or your answer is yes?

Mr. GOLDHAMMER. Well, I am saying I don't have an answer, as PhRMA right now.

Mr. WAXMAN. And I don't have anymore time.

Mr. PALLONE. Thank you. Thanks a lot. OK, next is Mr. Buyer.

Mr. BUYER. Thank you, Mr. Chairman. Mr. Thew, I want to thank you for being here, but when you leave today, I would like for you to bring a point up with the leadership of ALS and other patient advocacy groups, that these groups were pretty silent during the Democratic majority's effort to repeal the noninterference language that would have had a detrimental impact upon many narrow-targeted drugs that help many different narrow-disease groups. So I just want you to take that back with you. I appreciate you being here to testify on this issue, but their silence on this other issue was painful to me. And so I appreciate you being here today and take that up with them and tell them don't play politics when it comes to your friends who are similarly situated.

With regard to PhRMA and BIO, let me ask this question. The witness on behalf of FDA did not do a very good job, I don't think, answering questions that I had or Mr. Pitts or Mr. Rogers, relative to this question of the prevalence that we have right now on the drugs that are coming into our ports of entry through these imported parcels. And so when the FDA and Customs do these blitzes and do the inspections, the prevalence of FDA unapproved drugs and biologics is shocking. And so from a curious standpoint here, as we talk about PDUFA IV and modernizing with regard to post-market review and we have got this escalation of adverse reports, how do we nail this one down? I mean, if I'm a manufacturer out there, I have got some pretty strong concerns with regard to these adverse reports and whether or not it is my drug or not. I mean, you could have Dr. Burgess here prescribe something for me, but then if I go, well, I am just going to get from a Canadian source and I come back and see him and say I don't feel any better, he may or may not report. Mr. Pitts asked a really great question. What more should we require of doctors to ask of the patients, where did you get that prescribed drug from? Did it even have proper labeling? Did it come from an approved source? I am curious about your impression of all of our questions. What do we need to add in this legislation, if anything, to nail this down?

Ms. HOLCOMBE. Well, I don't know if there is something that you specifically can add into this legislation. But alliteratively, I would like to share your shock. We have been strong opponents, for years, of efforts to reduce FDA's ability to track imported products that are not approved by the agency, to go after these products, prevent them from reaching consumers in the United States, prevent counterfeit drugs from coming in. And most of the products that BIO

member companies produce are products that are injected and so they come in vials. Mostly they are clear liquids. So if you get a clear liquid in a vial and you take a syringe full of it out and inject into a patient, there is no way for you to know, is it the thing? Is it not the thing? Is it clean, dirty? And we have had very well-publicized incidences exactly as you have described, where patients have taken the drug over and over and they are not getting better. We believe the wrong message has been sent to FDA by attempts to legalize the importation of prescription drugs and that this is something that we find shocking and appalling, that this should go on. This is dangerous, it is absurdly dangerous and yes, from the innovative company's perspective, we do wonder how many when we see these escalations of adverse reports. Is this our product? Or is this something that someone else is shaking up in a garage somewhere and sticking into our bottles? So I am shocked.

Mr. BUYER. Thank you.

Mr. GOLDHAMMER. Yes. And I think our other major disappointment, in addition to what Ms. Holcombe said, is with FDA's inability to finalize the pedigree regulations that is called for under the Prescription Drug Marketing Act that was introduced by Congressman Dingell some years ago, because this would then provide the assurance of completely keeping the supply chain within the United States closed. We have tried doing as much as we can, through a variety of media opportunities, to make sure that patients purchase drugs through established pharmacies or Internet pharmacies that are verified by the National Association of Boards of Pharmacy, to make sure that they are not getting something through some kind of phony Canadian Web site.

Mr. BUYER. Thank you, Mr. Chairman.

Mr. PALLONE. Thank you. Chairman Dingell is recognized for 5 minutes.

Mr. DINGELL. First, thank you. I would like to welcome our distinguished panel here and tell them that we very much appreciate their assistance. I want to express my particular affection and respect for Ms. Holcombe, who did such valuable work when she was a very fine member of the staff of this committee, particularly on matters like PDUFA. Welcome back, Ms. Holcombe. We are honored that you are with us. Thank you, Mr. Chairman.

Mr. PALLONE. Mr. Stupak.

Mr. STUPAK. Well, thank you and again, thank you for allowing me to ask questions. Mr. Goldhammer, in your testimony, you stated you believe that "PDUFA agreements substantially addresses all relevant recommendations made by the IOM." However, a very quick glance at the IOM report, I am unable to see where the proposal, where in the proposed recommendation by IOM, that there should be specific safety-related performance goals in PDUFA. That is not in there. Also, I cannot find where IOM's recommendation that CDER review teams, regularly and systematically, analyze all post-market results and make the public aware of their assessments or the significance of the results with regard to risk and benefit information. Don't you believe those two goals should be part of PDUFA IV?

Mr. GOLDHAMMER. I think you asked some very good questions that probably are better directed towards the FDA, in terms of what kind of internal management changes they are going——

Mr. STUPAK. Well, I can tell you that they don't know and you are at the table, so that is why I was asking you guys.

Mr. GOLDHAMMER. OK. Well, again, I am not an FDA employee and I would be loathe to comment on what are essentially FDA management issues.

Mr. STUPAK. No. But you were there. Weren't you guys there? PhRMA was at the table negotiating PDUFA IV with FDA. Don't you think these two goals should be in there, specific to safety-related performance goals?

And also post-marketing results that would be made available to the public so they can assess the risk benefit analysis of a drug they are taking.

Mr. GOLDHAMMER. Well, with respect to post-market study results, we already took the initiative on that several years ago when we set up a database for clinical study results and we have got data on over 350 drugs in that database.

Mr. STUPAK. Those are only the studies you want to put on. They are not all the studies. It is the only one that PhRMA and the manufacturer puts on. It is not the ones that may find an adverse event. You control the information that is going on there. What we are asking for is all the reports be made available so the American public can decide. Don't you think that is a good idea?

Mr. GOLDHAMMER. Well, again, I think those are questions that Congress should deliberate and there should be a thorough consideration of those as you move forward.

Mr. STUPAK. Mr. Vaughan, do you care to comment on that?

Mr. VAUGHAN. We desperately need those, sir, and we find it is strange that we complain about the high cost of developing drugs and bringing drugs to market and yet people don't want to provide information on what trials were done and what the results were so that as a result, people keep repeating dead-end efforts of other companies. Not only that, but it hides safety features, so we desperately need a reform of the clinical trial registry and results database, sir.

Mr. STUPAK. Mr. Vaughan, I had asked Dr. Mullin, the last panel, about the $29 million, and Mr. Waxman mentioned a little bit about it, too, which I see represents a mere 7 percent of the user fees paid by industry to FDA to be put in post-marketing surveillance. Do you feel this is enough?

Mr. VAUGHAN. Not at all. There is good news in this Kennedy-Enzi bill being marked up tomorrow. As introduced last week, it was $70 million more. The version they put out tonight is $50 million more, but that is a good deal. That is better than the $29 million. We think even more is needed, sir. In fact, in the written testimony, we have a list of a bunch of projects that if you all would care to consider and legislate and help fund, we would have not only the fastest approval system in the world, we would have the safest drugs in the world.

Mr. STUPAK. Now, Mr. Vaughan, you also mentioned Rozerem and that was a sleeping pill ad that ran in September 2006, where Rozerem would remind you that it is time to go back to school. This

ad was complete with visuals of chalkboards, school books, school bus, laptop computers, school-age children with their backpacks. It is my understanding that it took the FDA more than 6 months to ask this drug maker to cease these ads that suggest sleeping pills are indicated for children. I find that simply outrageous and indicative of the problems that plague the FDA. Yet, in the Administration's newly released PDUFA reauthorization proposal, FDA recommends creating a separate user fee program to collect fees from companies that seek FDA advisory reviews of their direct-to-consumer television prescription drug advertisements. Do you expect a voluntary program that allows drug makers to decide if they want their advertisement clear will have any major effect?

Mr. VAUGHAN. That is what baffles me and I hope you all can dig into that a bit, because if you don't get anything more than a letter 6 months later saying please stop or tell us when you are going to stop—and of course they had stopped in early September—why would you bother with this volunteer program. And Consumers Union and Consumer Reports magazine, we have documented a major decline in penalty letters. So they are telling companies that they are not doing as good a job monitoring these ads. There is no penalty when there is a violation. Why would you pay a user fee? I am just not sure that idea works, and I hope you all can kind of dig into what brings you to the table to use this service to get an honest ad out there.

Mr. STUPAK. So would you support IOM's 2-year moratorium, then, on direct-to-consumer advertising until we can try to straighten this out?

Mr. VAUGHAN. On drugs where there is some background chatter or it is a new drug, wherethere might be a problem? Absolutely. I keep this pinned to my wall. It was an ad that was done in a newsletter, not you and I, but to executives of drug companies and it says, "how many prescriptions...how many weeks in market...until you are confident that your drug is safe" Why do we want people out mass advertising when this is what the businessmen themselves are saying. "I don't know, but maybe once 10 million people use it we will know." If they are going to advertise, there ought to be a little sign up there that says, and you are participating as a human guinea pig. Call 1–800-FDA if there is an adverse effect.

Mr. PALLONE. Thank you.

Mr. STUPAK. Thank you.

Mr. PALLONE. And I apologize for missing you, Dr. Burgess. I recognize you for 5 minutes.

Mr. BURGESS. That is OK, Mr. Chairman. It has been a long day. I appreciate everyone staying with us through all of this. Dr. Goldhammer and Mr. Hubbard, I was so glad that you are here to give the perspective of what life was like before PDUFA, because some days I wonder if I really remembered it accurately. But as a clinician during the 1980's, it just seemed like we were constantly running behind trying to get new therapeutics to our patients. In fact, we had a whole course of medical school called developmental therapeutics for cancer drugs, which was designed to how do you get around the FDA? I guess I shouldn't go into that too much now. But let us talk about the direct consumer advertising. Again, I am not a fan of it. We heard testimony in the previous panel that two-

thirds of the direct consumer advertising, there were two-thirds that did not go through the voluntary. Dr. Goldhammer, do you have a sense of that two-thirds, in retrospect, how much of that advertising would seem to be a problem, that is if a company did not self-refer of the two-thirds that did not self-refer, what segment of that two-thirds of the population ended up doing something that perhaps shouldn't have gotten on the airwaves?

Mr. GOLDHAMMER. Well, a number of those may not have been self-referred. It may have been just minor changes to an existing ad campaign, and the PhRMA principles don't call for those to be submitted for pre-clearance if they are minor changes, because it is up to the company to make that decision. Again, I think the most telling is the FDA statistics that point out that there have been very few enforcement actions against television ads and we like to think that is because of the PhRMA principles being put into place. The other thing that the PhRMA principles call for is in the case of a new drug that has just been approved, is that no direct consumer advertising take place until the company has had a chance to go out and do an educational campaign with physicians, so physicians don't end up getting blindsided by drugs out on the market and patients are coming in holding the ad.

Mr. BURGESS. Yes, you assume we are paying attention and of course the practice of medicine has changed in the 21st century and patients aren't the same patients that were there in the 1990's and the 1980's, and as much as I don't like direct-to-consumer advertising, there were times where patients brought me information of which I was not aware and after further research decided that this would indeed be an appropriate therapy for them. And again, it may not have crossed my mind or I may not have been as up on it as I should have been.

Let us talk just a little bit about the user fee/appropriation ratio, and this is really for everyone on the panel. We have Mr. Thew, whose primary goal in being here today is that we do not obscure a therapy or delay a therapy that could come his way and for people who are similarly afflicted, and I share his prayer in that regard. But I don't recall anything, Mr. Chairman, and maybe I am wrong, but we passed a big budget here a few weeks ago and I don't recall anything in there that had a big increase in the amount of money we were going to give the FDA. Now maybe I missed it. Maybe it was in one those vaunted reserve funds, but to the best of my knowledge, those reserve funds were not funded with actual dollars. They were more like, well, let us send a get well card to SCHIP and maybe we sent a get well card to the FDA.

But if we are really serious about it and if that is going to be the point of the discussion today, then, clearly, people on this committee need to pay attention when we go through our Labor, HHS appropriation bill, and if the Appropriations Committee has not done its work that we offer, the appropriate amendments under an open rule, and I know that means we stay up here all night, but that is OK, to see that you get the funding in the appropriations process to balance the money that you are going to get in the PDUFA process. And I have heard various figures, but the proportion that I am going to take away from here is a 50/50 mix. Is that about the right number or do other people feel differently about

that? Mr. Vaughan doesn't want any, but again, I remember the 1980's. I am not going back there. I know Mr. Thew doesn't want us to go back there, and you are about 15 years too late for that and I would respectfully suggest that it was a Democratic Congress that was here 15 years ago. So when you lost that battle, actually, your friends were in charge here. But am I correct on that, that it should be a 50/50 mix on the appropriation PDUFA funding?

Mr. HUBBARD. Well, may I comment, Dr. Burgess?

Mr. BURGESS. Please.

Mr. HUBBARD. When the 2007 budget was passed a few weeks ago, FDA needed $90 million just to keep even from where it was in 2006. They got $88 million. So they basically stay flat and that was the best budget they have had in recent years. So the environment is such that a flat budget that says you can do no more is good, because they have been actually losing money every year for the last decade.

Mr. BURGESS. Well, we have level-funded our doctors for the last 5 years, so I know it seems appropriate that we do the same to the FDA. Well, I appreciate everyone being here. I know my time has expired, Mr. Chairman, and I appreciate your indulgence. Just one last thought. Mr. Hubbard, the comments that Mr. Buyer was making, do you have any sense as to what this—if you recall, he called it an exponential rise. Do you have any sense as to whether or not any of those adverse drug reactions are because of corruption of the supply chain from foreign interference?

Mr. HUBBARD. No. As you know, Dr. Burgess, the counterfeiting is endemic around the world. The United States has been relatively free but it is increasing in the United States, both by people wanting to sell large volumes of counterfeit drugs, as well as these imported drugs supposedly from Canada and elsewhere. But because these drugs are not supposed to be here and they are not legal drugs, the healthcare system doesn't have a way to track them, because there is no way of knowing that they are even here and how to track them. And of course, FDA has no resources to go to doctors and medical centers and develop a tracking system for these drugs that shouldn't even be here to begin with.

Mr. BURGESS. So these adverse drug reports could include——

Mr. PALLONE. We are over our minutes, so wrap it up.

Mr. BURGESS. Yes, but you ignored me, so I am taking it out on you now.

Mr. PALLONE. That is true. That is why I am being good.

Mr. BURGESS. This graph could include counterfeit but it may not, so we have really no way of evaluating that.

Mr. HUBBARD. It could. It probably doesn't. These are so-called manufacturer reports where a doctor reports to the drug sponsor and then they report to the FDA.

Mr. BURGESS. So we should accept this at face value?

Mr. HUBBARD. Well, most of them, I think.

Mr. BURGESS. All right, thank you.

Mr. PALLONE. Thank you and that is the end of our questions, but I really thank you all for being here. I thought it was—oh, I am sorry, Mr. Dingell. I apologize. Go ahead.

Mr. DINGELL. I have just one other question I would like to ask of the panel here. And if you would bear with me, Mr. Chairman,

I would be very appreciative. Mr. Hubbard, your statement, I thought, was a very helpful one and I thought your comments on the success of PDUFA were very beneficial. Just to give us a little history several years ago, we found that there were severe problems related to the FDA prescription drug program. This committee had to run an investigation, which led to the indcitment of a fair number of individuals at the Food and Drug Administration. One of the things we found was that the Agency didn't have the money that it took to process prescription pharmaceutical applications by the pharmaceutical manufacturers. We found that people were coming to the judgment that they were going to favor this applicant over that applicant and sort of play god. Gratuities were passed and all kinds of bad things happened.

So we had two problems here. We had a terrible climate inside FDA. As I mentioned, it resulted in a few good individuals going to jail. We also had the problem that there was not enough money to process new drug applications in a timely manner. So there were several things that flowed from that. The first was that the applications were not approved and as a result, drugs that could have helped people were kept off the market. The other thing was that manufacturers could not get decent service. So we began a process of negotiating with the manufacturers and we said, look, we are going to get you a system whereby you pay for the service, and they found that this was a very good buy, because of what they received in return. They made a huge amount of money by shortening the time of waiting for approval by the Food and Drug Administration. It worked so well that we were able to engage over-the-counter drug manufacturers. Because they found that this was important to them. And then, after a long period of negotiations, we engaged medical device manufacturers and we found that all of this worked. We gave a commitment to the manufacturers that we would protect their user fee money so it would not be diverted.

Now every time this committee writes legislation to put in the trust fund, and I don't care if it is us or the Public Works Committee or any of the other committees around here, we find that the appropriators in the Office of Management and Budget and the budgeters try to divert those user fee monies. Your comments indicated that PDUFA has been a tremendous success, but you also indicated that because more than 50 percent of the FDA drug approval budget comes from manufacturers for the licensing process, that there is some kind of corruption, at least that is the impression I come away with. I want to know, is there some dishonest practice? Is there corruption at FDA? Is there something going on down there that this committee needs to look into? Now, tell me.

Mr. HUBBARD. Well, you will recall, Mr. Chairman, you are referring to a generic drug scandal that occurred in the late 1980's, in which you and your committee uncovered that. There have been examinations of the new drug approval process, to look for that. It has never been found. And one of the advantages of the new drug approval process is there are so many physicians and pharmacists and others involved at FDA, that one person can't have much influence. So fortunately, that program has been free of taint, at least that is widespread perception.

Mr. DINGELL. Well, if there is wrongdoing down there and if this is tainting the system, we will change it. And I am asking you, is this creating a problem in terms of the integrity of the system, in terms of the protection of the consumers, in terms of the integrity of the Food and Drug Administration?

Mr. HUBBARD. It has clearly been a concern on the part of FDA leaders and staff that the fees should not continue to go up because it could potentially lead to a problem.

Mr. DINGELL. Is that a statement supported by evidence of misbehavior and wrongdoing? Or is that statement based on a theory of how good government should really work?

Mr. HUBBARD. I think the latter. There is no evidence of wrongdoing, but certainly the perception, as Mr. Vaughan and others have pointed out, when the industry starts paying 70, 80 percent of the fees——

Mr. DINGELL. Well, let me express one of my concerns. We investigate and analyze and check out the safety of less than 1 percent of the foods coming into this country. We import about 50 percent of our foods. Customs charges for the review by Customs agents at the point of entry. They have numerous agents, so the process is expedited. The Food and Drug Administration currently does not provide the same reviews for food at the points of entry. FDA fails to inspect the foods we import. Now what is coming in? Fruits and vegetables contaminated; dog food or cat food with melamine in it; a significant problem in terms of bacterial and viral contamination of food stuffs coming in; tremendous amounts of counterfeit and illegal pharmaceuticals are being imported into the country. No way of stopping it; no way of dealing with it. The good hearted people at the Office of Management and Budget believe food inspections are not needed. We have a leaner, meaner Food and Drug and they do a splendid job on this. And then I go back and talk to Food and Drug and they say, well, how many of these things are you connecting, and how many cats and dogs got killed just recently by bad stuff coming in from China? And so they have to admit, well, we aren't doing so good.

Now what are we going to do about this? You live in a system where money is like this or diverted and we have had—time preserving and protecting the monies that have to go to see to it that PDUFA is properly implemented. Now, if PDUFA is not being properly implemented, if there is dishonesty, misbehavior, bribes, or special preference being afforded, I want to know about it. If there is not, then I have to say, if we are going to continue this system and we are going to try and do the best we can about making it work, in the broad interest of the public and the broad interest to the industry and the broad interest to the consumers and in the broad interest of good government. Now is there rascality and if so, who is doing it and what is doing it? What is happening? What do we have to do about it?

Mr. HUBBARD. Mr. Chairman, I remember that you were sitting in that chair 21 years ago, 1986, and I was on this side and you said imports are a scandal and FDA was inspecting 10 percent at the time. Today, they are inspecting less than 1 percent. The oversight of imported foods is a catastrophe and I will agree with you all day long on that. In terms of PDUFA, I don't see the kind of

scandal you are raising in that program. They are very hard-working, dedicated people, but they do need more resources.

Mr. DINGELL. And this committee spends a huge amount of time trying to get it for them and I must say, only with modest success. Now, I want to thank you, Mr. Hubbard. I have asked you some hard questions. If you come upon any wrongdoing, I want to be the first to hear about it, and the committee wants to hear about it. We will have the appropriate individuals before the committee to answer questions about what they are doing that isn't right.

Mr. PALLONE. Thank you.

Mr. DINGELL. Mr. Chairman, I thank you.

Mr. PALLONE. Thank you, Mr. Chairman. Mr. Markey is recognized.

Mr. MARKEY. I thank you, Mr. Chairman, very much and I thank you for your courtesy. Could we just go down yes and no on this? The question is, should the FDA have the authority to require post-market studies, as recommend by the Institute of Medicine and by the Government Accountability Office? Just go down. Should the FDA have the authority to require post-market studies? Mr. Goldhammer?

Mr. GOLDHAMMER. Yes, I think, again, I will have to give the same answer.

Mr. MARKEY. Could you just answer yes or no?

Mr. GOLDHAMMER. We are not prepared to answer that question yes or no.

Mr. MARKEY. You are not prepared to answer it. Yes, Mr. Hubbard?

Mr. HUBBARD. Speaking for myself and not for the group I am representing, yes.

Mr. MARKEY. Yes. Thank you. Mr. Thew?

Mr. THEW. I would say yes.

Mr. MARKEY. Yes. Thank you. Ms. Holcombe?

Ms. HOLCOMBE. Speaking only for myself, yes.

Mr. MARKEY. Yes. Thank you.

Mr. VAUGHAN. Absolutely, yes. And for Consumers Union, absolutely, yes.

Mr. MARKEY. Thank you. And I thank each of you for that. Mr. Vaughan, would anything in this Bush administration proposal prevent selective disclosure of clinical trial results and ensure that the public has access to all clinical trial information by creating a mandatory registry of a clinical trials and results database?

Mr. VAUGHAN. No, sir.

Mr. MARKEY. What is the problem with that?

Mr. VAUGHAN. We are absolutely for it and it is in your bill with Mr. Waxman, and Kennedy-Enzi, but correct me if I am wrong, but the PDUFA draft bill up from the Administration doesn't do anything in that area.

Mr. MARKEY. Why is it important that it do something in that area?

Mr. VAUGHAN. Well, we would know what people have found about the safety of a drug and even more, I think, sometimes what they like to hide is whether it is any better than a placebo.

Mr. MARKEY. OK. Again, Mr. Goldhammer, would you support having mandatory language that all clinical trials have to be on a list?

Mr. GOLDHAMMER. Again, that was not the province of what we were permitted to discuss during PDUFA. I understand there would be a subsequent hearing in this subcommittee on drug safety and that would be part of it and I am sure we would be happy to come back to you with an answer. But my answer right now is we have stepped up to the plate and created such a database, which is already being utilized.

Mr. MARKEY. But your database, Dr. Goldhammer, is a voluntary registration.

Mr. GOLDHAMMER. That is correct.

Mr. MARKEY. Yes. Now, if a company doesn't want to voluntarily provide all clinical tests, what is the penalty which you impose upon them?

Mr. GOLDHAMMER. Well, you hit it right on the head, it is voluntary and we, as a trade association don't have an enforcement mechanism.

Mr. MARKEY. So there is no penalty?

Mr. GOLDHAMMER. Correct.

Mr. MARKEY. Right. So the effect of that is that they can, like I would have liked to have done when I was a boy, bring home the good marks I got and not have to bring home the bad marks to my mother and father. But the world really doesn't work that way or the world doesn't work well that way. We can hide the tests that you fail. The only way in which there is any accountability is if all of it is disclosed. So let me go over to you, then, Mr. Vaughan. Could you comment upon that, that PhRMA, this whole idea that PhRMA has that you kind of grade yourself? You pick the stuff that you want to make to public.

Mr. VAUGHAN. Oh, we think it is an absolutely terrible problem, in that most of the trials that do get published in the big journals are favorable to the person who paid for the trial. It is a pretty rare day that you get a trial published that isn't favorable to the person who is, again, paying the bill. And to get real honesty, we need to know what was to be studied, what the end points were, and then what the results were, because it can get written up in ways that puts lipstick on a pig.

Mr. MARKEY. Well, let me ask you, Mr. Hubbard. Do you think that they should be able to selectively pick the trials they release or should they have to release them all?

Mr. HUBBARD. Certainly full disclosure would be the best thing.

Mr. MARKEY. Full disclosure would be the best thing. Mr. Thew?

Mr. THEW. I would have to say I am not really too sure on that, sir.

Mr. MARKEY. You are not too sure on that? OK. Ms. Holcombe? So good to see you, by the way.

Ms. HOLCOMBE. I am not going to give you a yes or no on this globally, but I do want you to know that it is the policy of Genzyme Corporation, a Massachusetts company, to register all of our clinical trials in accordance with the rules and to publish the results of all of our studies, generally, in accordance with the principles that were laid out in your previous legislation.

Mr. MARKEY. OK, I thank you for that. So that then, Mr. Chairman, it puts us in a situation where, again, you have PhRMA down here sitting isolated and I understand that position. It is a position, however, that leads to serious risks that the public and, in fact, physicians could be misled by the selective information which is provided to them, that they don't have access to all of the clinical trials. And there is no penalty. The risk is run by the patients, by the physicians, but there is no penalty for the companies. And I think that Ms. Holcombe, in talking about Genzyme, is talking about a company who has accepted that and knows that there is a responsibility. And I don't think, honestly, that we shouldn't finish this process without ensuring that the public gets the information they need. If PhRMA opposes this legislation based upon that, then there is something fundamentally wrong with PhRMA. This voluntary system just can't continue because of the danger to patients. And we go back through Paxil, but we can't go back through so many other instances where information was withheld that would have been of very critical importance to families. It just can't be selective. You have to know it all, because the decisions which people make have to be informed decisions. And I look forward to working with my colleagues to return the FDA to its role as a watchdog for the health of our country, and I hope, through this process, we are able to accomplish that goal and to put those safeguards in place. And I thank each of you for testifying and I yield back the balance of my time. Thank you.

Mr. PALLONE. Thank you very much, Mr. Markey. I am going to look around again and make sure we have no additional people coming. But that concludes our questions and thank you all for being here. I thought it was very useful to hear your testimony and the back and forth. I just wanted to remind members that they may submit additional questions, for the record, to be answer by the witnesses and the questions should be submitted to the committee clerk within the next 10 days, so you may get additional questions to answer. And without objection, this meeting of the subcommittee is adjourned.

[Whereupon, at 2:05 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

May 21, 2007

Theresa M. Mullin, Ph.D.
Assistant Commissioner for Planning
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Mullin:

Thank you for appearing before the Subcommittee on Health on Tuesday, April 17, 2007, at the hearing entitled "Reauthorization of the Prescription Drug User Fee Act." 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 Members who have 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 **Monday, June 4, 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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

The Honorable John D. Dingell
Chairman
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

JUL 9 2007

Dear Mr. Chairman:

Thank you for the opportunity to testify at the April 17, 2007, hearing entitled, "Reauthorization of the Prescription Drug User Fee Act (PDUFA)," before the House Committee on Energy and Commerce, Subcommittee on Health. Theresa Mullin, Assistant Commissioner for Planning, testified on behalf of the Food and Drug Administration (FDA). We are responding to the letter of May 21, 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 Representatives Mike Ferguson and Michael Burgess on the following separate pages.

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

Question from The Honorable Mike Ferguson

The Subcommittee has been informed of an unintended result of PDUFA that may be discouraging the development of an important class of radioactive diagnostic imaging drugs—the positron emission tomography (PET) drugs. PET drugs are an important tool for detecting various malignancies, as well as for diagnosing epilepsy, cardiac and bone disease, and other life-threatening conditions and promise to be similarly important tools for the Food and Drug Administration (FDA) Critical Path Initiative. Since PET drugs have a maximum radioactive half-life of several hours, they are produced in cyclotron facilities in close proximity to the medical centers where they will be administered to patients. As a result, unlike conventional drugs, their preparation and distribution is necessarily decentralized and small-scale. We have been informed by PET producers that, to supply a PET drug nationally, requires approximately 50 cyclotron facilities nationwide.

Under a temporary moratorium established pursuant to section 121 of the FDA Modernization Act of 1997, PET drugs may be produced and marketed for several more years without submission of a New Drug Application (NDA). However, once the moratorium ends, each NDA for a PET drug, similar to other NDAs, will have to identify each establishment in which the drug is manufactured and pay an annual fee for each establishment under PDUFA. Since a commercial manufacturer that supplies PET drugs nationally, or even regionally, requires many manufacturing establishments, this could result in enormous fees annually.

FDA has recognized this problem, and has proposed to amend PUDFA in a manner that would reduce the establishment fee payable by a PET drug sponsor to 25 percent of the fee applicable to other drugs. The Senate Health Education Labor and Pension Committee has incorporated this relief in their current draft bill. However, I am concerned that, in light of the expected revenues of most PET agents, this establishment fee burden could still dissuade sponsors from developing and seeking approval for new PET agents. A sponsor that intends to distribute a PET agent nationwide using the necessary 50 cyclotron facilities would still have to pay the equivalent of 12.5 full establishment fees. In comparison, sponsors of other drugs, including the largest ones, typically pay only one, two, or three establishment fees.

Under fiscal year 2007 rates, 12.5 fees would amount to $3.9 million in establishment fees annually for diagnostic drugs that, we are informed, may anticipate annual revenues on the order of only $5 to 10 million if distributed nationwide. Of course, the actual fee rates will be higher in the future.

- **I would be interested in understanding FDA's proposal to apply roughly the equivalent of 12.5 establishment fees or $3.9 million in annual fees on such products and why this establishment fee would not still be a burden to innovation and dissuade sponsors from developing and seeking approval for new PET agents for the diagnosis and treatment of cancer, Alzheimer's and other life-threatening diseases?**

Page 3 - The Honorable John D. Dingell

Response to Question from Mr. Ferguson:

FDA will bear certain expenses associated with inspecting the various PET establishments. If there are 50 PET establishments, FDA will have to inspect each one periodically. These inspections must be supported, in part, by PDUFA fees.

This issue is not a question of how much FDA will collect, but rather how to distribute the costs of supporting the human drug review program. FDA will collect target revenues established in accordance with the statute, regardless of how many establishments are assessed fees. If fewer PET establishments are assessed fees, then other payers of user fees will pay a larger proportion of the fees, in effect subsidizing PET producers.

The PET industry has expanded significantly since 1997. At the time of passage of the FDA Modernization Act, there were estimated to be about 70 producers of PET products. Now, according to industry figures, there are between 141 to 151 cyclotrons. Only a few of the PET manufacturers are large, commercial entities that have multiple establishments, and nationwide aspirations. Generally, these are large multi-national corporations with substantial assets and revenues.

The pending legislative proposal in the Senate already reduces the fees by 75 percent. We do not believe a 25 percent establishment fee would be a significant disincentive to the development of PET products. If a decision were made to have the rest of the pharmaceutical industry subsidize further reductions in these fees, FDA would not oppose it.

Question from The Honorable Michael Burgess

What is FDA doing to monitor off-label uses of therapeutic drugs? Is there any interaction with companies that do not want their drugs used off-label?

Response to Question from Mr. Michael Burgess

FDA does not have a formal program to monitor off-label use. We can put information in the labeling warning about safety concerns associated with off-label uses when appropriate. Such circumstances would occur when the drug is commonly prescribed for a disease or condition, there is lack of substantial evidence of effectiveness for that disease or condition, and such usage is associated with serious risk of hazard.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

The Honorable Frank J. Pallone, Jr.
Chairman
Subcommittee on Health
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

AUG 15 2007

Dear Mr. Chairman:

Thank you for providing the Food and Drug Administration (FDA or the Agency) the opportunity to testify at the April 17, 2007, hearing entitled, "Reauthorization of the Prescription Drug User Fee Act," before the Subcommittee on Health, Committee on Energy and Commerce. During the hearing, the Agency's witness, Dr. Theresa Mullin, Assistant Commissioner for Planning, told the Committee that she would provide certain responses for the record. On July 9, 2007, we responded to written questions for the record, which you provided to us in a May 21, 2007, letter. In addition, we have reviewed the transcript from the hearing and set forth additional questions below in bold followed by our responses.

The Honorable Frank Pallone

1. "[Do you have] a date certain as to when [FDA] would be forced to send a reduction in force or RIF notice to FDA employees should the user fee program fail to be authorized before September 30?" (Transcript, p. 57).

FDA responded to this question by letter dated April 30, 2007. We are enclosing a copy of this letter.

2. " ...according to the data analyzed by Harvard professor Daniel Carpenter, drugs approved just before PDUFA deadlines are far more likely than those approved at other points in the review cycle to cause safety problems after they are in widespread use. Do you agree with that assessment? ... What I am trying to get at is whether there is any indication that PDUFA timeliness and PDUFA timelines compromise the safety of new drugs and biologics... Do you have any evidence you could submit to us in writing that would contradict what the professor is saying?" (Transcript, pp. 59-60).

We believe the paper noted above is titled, "Deadline Effects in Regulatory Drug Review: A Methodological and Empirical Analysis," Working Paper WP-35, February 2007, published

by the RWJ Scholars in Health Policy Research Program (referred to hereafter as Carpenter et al..) This paper is described by its authors as an elaboration on two sets of statistical models for the analysis of regulatory review "deadlines" and their influence on regulatory decisions. The paper appears to make two main points: 1) drug approval decisions "pile up" right before Prescription Drug User Fee Act of 1992 (PDUFA) review goal dates; and 2) new molecular entities (NME) receiving standard reviews approved in the 6-8 weeks before the PDUFA goal date are more likely to have post-market safety events compared to "drugs approved at other times in the review cycle."

Although the authors do not provide enough information to permit the reader to fully analyze their study or attempt to replicate their analysis, we believe we can respond to their general assertions based on our own data. In general, we are not surprised by the "pile up" described in the paper (i.e. of Agency decisions shortly before PDUFA review goal dates), but we believe that this circumstance has no implications for drug safety. Our own data do not support the existence of a causal link between approvals made close to the review goal and post-market drug safety events. It is important to note that it is impossible to anticipate virtually all post-market safety events prior to marketing approval given the limited information available through clinical trials. Post-market safety issues are usually uncovered only after hundreds of thousands of patient exposures.

Regarding their first point, Carpenter et al.. report finding that drug approval decisions "pile up" right before PDUFA review goal dates. This is precisely the pattern one would expect if FDA were meeting review performance goals. Under PDUFA, FDA committed to perform a complete review and provide a complete response to the sponsor within a specified period of time. This commitment to providing complete and timely feedback has been critical to the success of PDUFA in reducing the average time to approval for new drugs. In the early years of PDUFA, which started in fiscal year (FY) 1993, FDA developed an improved process with better management and resources to meet this commitment. See Table 1.

Table 1

Fiscal Year	Original NDAs, PLAs and ELAs*		
	Review and Act on Original NDAs, PLAs and ELAs Within 12 months		
	PDUFA Performance Goal	Percent on Time	Goal Met (Y/N)
1996	80 %	96 %	Y
1995	70 %	95 %	Y
1994	55 %	93 %	Y
1993	n/a	63 %	n/a

*NDAs (New Drug Applications), PLAs (Product Licensing Applications), and ELAs (Establishment Licensing Applications); PLAs and ELAs were later replaced by BLAs (biologic license applications).

By FY 1997, the final year of PDUFA I, FDA committed to review and act on 90 percent of priority NDAs within 6 months, and 90 percent of standard NDAs within 12 months of receipt of the application. During PDUFA II, FDA retained the same goal timeframe for priority reviews and transitioned from a 12-month to a 10-month timeframe for standard NDAs. See Table 2.

Table 2

Fiscal Year	Priority NDAs/BLAs		Standard NDAs/BLAs	
	Review and Act on 90 Percent of Original NDAs and BLAs Within 6 months		Review and Act on 90 Percent of Original NDAs and BLAs Within 10/12 months	
	Percent on Time	Goal Met (Y/N)	Percent on Time	Goal Met (Y/N)
2006*	95 %	Y	100 %	Y
2005	89 %	N	99 %	Y
2004	97 %	Y	97 %	Y
2003	100 %	Y	100 %	Y
2002	100 %	Y	99 %	Y
2001	100 %	Y	98 %	Y
2000	97 %	Y	97 %	Y
1999	100 %	Y	100 %	Y
1998	100 %	Y	100 %	Y
1997**	100 %	Y	100 %	Y
1996	Goals not separate (see Table 1).			
1995				
1994				
1993				

* As of September 30, 2006.
** FDA did not have separate performance goals for priority versus standard applications in FY1997, the final year of PDUFA I, but data related to these goals were available and were reported for FY 1997 in the FY 1998 report.

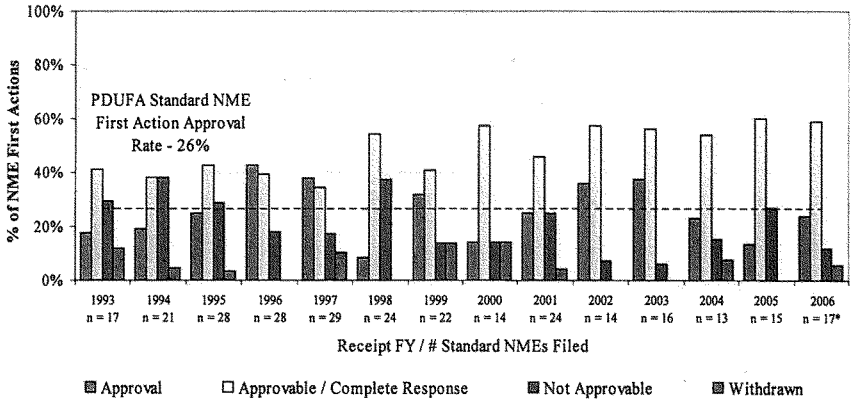
FDA has taken the commitment to providing timely feedback very seriously, and we have generally met the goal of providing a complete "action letter" (i.e. reviewing and acting on the application) by the goal date. Following FDA's review of an NDA, the action letter will communicate FDA's decision, and that will be one of the following: 1) the new drug is approved for marketing, 2) the new drug is approvable if the sponsor can satisfactorily address the deficiencies listed in the action letter, or 3) the new drug is not approvable because of the list of deficiencies provided in the action letter.[1] In general, if the application does not receive an approval on the first cycle of FDA review, the sponsor may resubmit the application, addressing the deficiencies listed in the first-cycle action letter, and the resubmission will undergo another cycle of FDA review.

Of the three types of FDA responses for an NDA review, only a fraction of first-cycle action letters communicates approval decisions. Figure 1 below shows the distribution of first-cycle actions across the three different FDA responses for standard new molecular entities (NMEs), a subset of standard NDAs and the focus of much of the analysis and discussion in the paper by Carpenter et al.. It appears that Carpenter et al.. has included in their analysis only those drugs approved on the first cycle of review. In contrast with the implications of the

[1] Due to differences in regulations, FDA's responses for BLAs, which are also included within the process of human drug review, differ in part from those responses for NDAs. In the case of new BLAs, FDA will respond with either 1) an approval decision or 2) with a "Complete Response" that will provide the sponsor with a list of the deficiencies found during the review that would have to be satisfactorily addressed before the product could be approved for marketing.

Carpenter paper, Figure 1 below shows that most standard NMEs are not approved in the first cycle. Only about 26 percent of all standard NMEs are approved in the first cycle. Some applications (an average of five percent per year for the period 1993-2006) are withdrawn by the sponsor before FDA issues an action letter.

Figure 1. First Action Percentages for CDER **Standard** NMEs and New BLAs
by Fiscal Year of Receipt



The remaining 69 percent of FDA first-cycle decisions are not approvals. Meeting a PDUFA goal for an application typically involves an action letter from FDA to the sponsor describing application deficiencies. These actions also occur shortly (i.e. within 6-8 weeks) before PDUFA review goal dates, because of FDA's commitment to provide a timely review. These first-cycle decisions that are not approvals are not included in the Carpenter et al.. analysis. The omission of the majority of FDA first-cycle decisions from an analysis of "deadline effects in regulatory drug review" is an important shortcoming of this work, and possibly a failure to recognize the real focus of review goals—timely feedback, not approval. FDA meets its goal of 90 percent of standard NDAs/NMEs reviewed and acted on within 10 or 12 months of submission, and most of those first-cycle decisions are not approvals. The preponderance of non-approvals makes it difficult to understand how Carpenter et al.. can assert that the review goals create an "incentive for the agency to approve the drug."

Second, Carpenter et al..'s critical finding is that new molecular entities receiving standard reviews approved shortly before (defined by Carpenter et al.. as within 6-8 weeks) the PDUFA goal date are more likely to have post-market safety events "compared to controlled sets of drugs approved at other times in the review cycle." We are skeptical that a full review of all the data truly supports this finding.

We do not understand Carpenter et al..'s "controlled sets of drugs." FDA takes action on over 90 percent of NMEs within (not beyond) PDUFA goal dates. In addition, very few reviews are completed more than 8 weeks prior to the goal. This leaves a very small number of potential products upon which Carpenter et al..'s conclusions are based.

In addition, the authors provide very little detail on their definition of terms critical to results of their analysis. We do not know what they mean by "time to approve an NME" because we do not know how they account for multiple review cycles. The authors do not disclose the source of their data, nor do they list the NMEs included in their study. Without this information, we cannot replicate their results. Some applications receive goal extensions. This would seem to affect the true deadline faced by FDA reviewers, but we do not see how Carpenter et al.. accounts for this factor. Under PDUFA II, there were both 10-month and 12-month review goals, but we do not see how these dual goals are incorporated into the analysis. Without better information about Carpenter et al..'s data, methods, and assumptions, it is impossible for us to address the paper's conclusions.

In general, we are concerned that the paper's results may be based on a very limited and oversimplified understanding of the human drug review process. For example, it is not clear that the authors are aware of multiple-cycle reviews, although multiple-cycles are far more common among standard NMEs than single-cycle reviews. The authors appear to be unaware of the purpose and information content of manufacturing supplements. Moreover, the authors are silent on application quality. The quality of the application may be the most important determinant of first-cycle approval. Again, first-cycle approval occurs in only about 26 percent of applications.

Although we cannot provide a more detailed response to the analysis in the Carpenter et al.. paper, we can address the issue the authors are trying to examine in their analysis related to safety: whether faster drug review under PDUFA (the result of significantly better funding and Agency commitment to review process goals) has had an adverse impact on drug safety.

A recent analysis[2] of safety labeling published by the National Bureau of Economic Research has taken a comprehensive look at this issue. The analysis recognized that comparing the safety of prescription drugs over time is difficult due to the paucity of reliable quantitative measures of drug safety. Both the academic literature and popular press have generally focused on drug withdrawals as a proxy for the effectiveness of the drug safety system. This metric (included in the Carpenter et al. paper along with a wide range of other activities) is problematic because withdrawals are rare events, and they may be influenced by factors beyond a drug's safety profile. Instead, the analysis examined the incidence and timing of Black Box Warnings (BBWs) as an alternative metric for drug safety and risk management.

BBWs are warnings placed on prescription drug labels when a drug is determined to carry a significant risk of a serious or life-threatening adverse event. Using a data set that includes NMEs submitted to FDA between May 1981 and February 2006, and subsequently approved

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[2] "Black Box Warnings and Drug Safety: Examining the Determinants and Timing of FDA Warning Labels" NBER Working Paper No. 12803 *http://papers.nber.org/papers/w12803*

and marketed, the study analyzed the timing and incidence of BBWs. The analysis also used data on several drug characteristics likely to affect the probability that a new drug will receive a BBW. It was found that drugs receiving priority FDA review are more likely to have BBWs at the time of approval than NMEs receiving standard review. It was also found that early prescription volume and orphan drug status are associated with an increased likelihood of receiving a BBW. However, the analysis did not find a significant difference in the rate of BBWs pre-PDUFA versus post-PDUFA. A comparison of NMEs approved before and after the 1992 enactment of PDUFA did not reveal a statistically significant difference in the rate of BBWs. Critics of PDUFA maintain that reduced FDA-approval times under PDUFA have compromised drug safety. This comprehensive study of all NMEs submitted and approved between 1981 and 2006 found no empirical support for that contention.

In summary, we agree with the Carpenter et al. finding that most FDA approval decisions occur near the PDUFA goal dates, but the Carpenter et al. analysis does not extend sufficiently far because approximately 90 percent of all review decisions (not just approval decisions) occur by the PDUFA goal dates. This statistic, in demonstrating the Agency's thorough satisfaction of these goal dates, represents the point of having PDUFA performance goals and is a reflection of FDA's commitment to meeting those goals.

The Honorable Steve Buyer

1. "Do we know that of the 60 percent increase of adverse effects over the last three years, do we know the impact of the counterfeit drugs are having upon that number?" (Transcript, p. 71)

We know that adverse events are under-reported and we know from history that tolerating the sale of unproven, fraudulent, or adulterated drugs can result in harm to the public health. It is reasonable to expect that the illegal sale of drugs over the Internet and other illegal foreign sources and the number of resulting injuries will increase as these sales grow. We cannot determine the exact prevalence of drug counterfeiting in the U.S. but given the volume of prescription drugs in this country (3.6 billion prescriptions written annually) we know that it currently appears to be relatively rare in the legitimate drug distribution chain. Similarly, we do not know the exact numbers of adverse events related to use of counterfeit drugs, but, when they have reached American consumers, we know they have posed a threat to health – both in instances where the counterfeit drugs were contaminated and thus posed a direct threat to consumers and in instances where the counterfeits were sub-potent and therefore failed to treat the underlying condition for which they were consumed.

The Honorable Lois Capps

1. **"So the understanding that I have had, that there is a plan to exclude individuals from an advisory panel if they hold $50,000 or more in financial ties to the company or its competitor, that is only determined after the year?"**

2. **"I understand that there is a plan and I am kind of disheartened to have read just last week about an advisory for Arcoxia, which did, even though this proposal is under way, that particular panel included scientists with financial ties?"**

3. **"advisory panels are very influential, is that true?"**

4. **"I was assuming that it was under your jurisdiction, but so I would really appreciate a response to this. I think there is some concern that I have held about the importance, and maybe that could be part of my question that you will get back to me or somebody will, about the role that the advisory panel plays, then, in determining the approval. Is it just advice and to what degree is it advice?"**

(Transcript, pp. 92-93).

Advisory committees provide independent, expert advice on scientific, technical, and policy matters related to the development and evaluation of products regulated by FDA, such as human and animal drugs, biological products, medical devices, and foods. The advisory committee system enhances FDA's ability to protect and promote the public health and maintain the public trust by enabling the Agency to obtain the benefit of independent, professional expertise. Although advisory committees provide recommendations to FDA, final decisions are made by FDA.

FDA recently issued draft guidance that would, among other things, generally prevent advisory committee members from participating in advisory committee meetings when they have specified financial interests that exceed $50,000. (Draft Guidance for the Public, FDA Advisory Committee Members, and FDA Staff on Procedures for Determining Conflict of Interest and Eligibility for Participation in FDA Advisory Committees [March 2007])

Pursuant to our regulation regarding good guidance practices, we issued the document as draft guidance for comment and not for immediate implementation. We plan to take the comments into consideration when considering finalizing the guidance.

The Honorable Heather Wilson

1. Ms. Wilson: "What kind of retention bonuses are available for these kind of folks [for scientific and medical experts...reviewers] and what kind of salary do they, on average, get?" (Transcript, p. 109).

The type of appointment and occupational series determines whether or not an individual employee is eligible to receive a retention incentive or any other pay supplements (retention incentives, Physicians Comparability Allowance [PCA] and Physician and Dentist Pay [PDP]).

FDA's Center for Drug Evaluation and Research offers a 10 percent categorical retention incentive to eligible employees in the following categories: Medical Officers, Pharm/Tox Reviewers, Mathematical Statisticians, and Pharmacokinetics. Incentive amounts are calculated on annual salary. The salary ranges for these eligible employees span from a GS 13, step 2 up to a GS 15, step 10 and can average $134,164 to $157,818, which includes the retention incentive.

In addition to the 10 percent categorical retention incentive, Medical Officers are eligible for PCA, which is a Title 5 authority to recruit and retain physicians using additional compensation. PCA is authorized only to address demonstrated recruitment and retention problems. PCA amounts range from $1,000 up to $30,000 and the allowance amount is determined by the physician's grade level, education/experience, number of years as a Government physician, and length of the service agreement signed.

Another pay mechanism that is available for Medical Officers who have served at least 4 years of service within FDA is Title 38, PDP. The Title 38 pay authority allows compensation of physicians and dentists (full-time and part-time) at the GS-15 level and below who provide direct patient care, or services incident to patient care. It is designed, within budgetary constraints, to promote recruitment and retention of highly qualified physicians and dentists and to compensate these employees at levels reasonably comparable with those paid to other federal sector physicians and dentists in the same local area. Medical Officers cannot receive PCA if they are paid under the Title 38 pay authority. In addition, within FDA, Title 38 Medical Officers do not receive retention incentives.

HHS uses the Veteran's Administration pay tables and tiers to administer/set pay for Title 38 employees. The Veterans Administration Secretary prescribes nationwide minimum and maximum amounts of annual pay for seven pay tables and four tier levels covering a variety of clinical specialties and assignments. Currently, the minimum pay range amount is $90,000 and the maximum pay range amount is $295,000, with increase amounts to be effective July 22, 2007. The assignment of a physician or dentist to an appropriate pay table and tier level is based on the physician's/dentist's level of experience in the clinical specialty or assignment, the need for the specialty or assignment at the facility, board certifications, if any, accomplishments in the specialty or assignment, and consideration of unique circumstances, qualifications or credentials. Currently, FDA Title 38 Medical Officer salaries range from $148,274 to $235,884 with an average salary of $190,606.

The Honorable Mike Rogers

1. **"Because what concerns me is the World Health Organization estimated by 2003 that there were $32 billion of counterfeit drugs in the world market, which is about 10 percent. And in the U.S. value of counterfeit drugs seized in 2003 was $200 million which was a sevenfold increase in the year before. So when we look at a 60 percent increase in adverse effects between 1999 and 2003, and a sevenfold increase in counterfeit drugs between 2002 and 2003, you know, I used to be an FBI agent and scratched my head a little bit, but that is a clue. There is a problem growing here and I don't get a sense, at all, that the FDA – and how do you go through an efficacy plan when a doctor is writing in that gee, that drug didn't have any effect at all on my patient? Matter of fact, just down from my office in Lansing, Michigan, they did a raid in the Detroit area and found that insulin was not refrigerated correctly, wrong instructions were on the drug. This is one of those Canadian pharmacies that we found out was not a Canadian pharmacy. And non-active ingredients. So none of that, according to the testimony today, gets factored in at all. How can we honestly say we are coming up with a system for safety and efficacy even with post-approval, when we have no clue where the logistics chain of those drugs are?"**

2. **"But that is the only thing that concerned me, and I know my time is up, Mr. Chairman, is that that hasn't been already ruled in and how you would make that determination. Just in one port, they found that 85 percent of the packages they inspected, 85 percent that were labeled as Canadian drugs were, in fact, not Canadian drugs. That is a huge problem. And if you don't have a plan to roll that in to make that determination, maybe it is a 1 percent problem, maybe it is a 90 percent problem. The thing that scares me most is that you don't know."**

(Transcript, pp.118-20).

FDA uses a risk-based approach that uses our resources most efficiently and effectively. We continue to explore new approaches to keep violative products out of the U.S. closed distribution system. In 2003, FDA released the Counterfeit Drug Task Force Report, outlining a number of measures, including private/public partnerships, to combat counterfeit drugs and further secure our nation's drugs supply. Since then, FDA has been actively working with stakeholders to implement these measures. In addition, FDA created the Counterfeit Alert Network, a coalition of health professional and consumer groups and has a voluntary agreement with the Pharmaceutical Research and Manufacturers of America (PhRMA) to report suspected instances of drug counterfeiting to FDA.

Customs and Border Protection (CBP), Immigration and Customs Enforcement (ICE), other federal, state and local law enforcement, and public health regulatory agencies. OCI also coordinates counterfeit drug investigations with several foreign counterparts, especially those in China, Israel, the Netherlands, England, and Canada, to enhance criminal investigations. These efforts continue to produce positive outcomes for both OCI and its foreign counterparts. OCI will continue to aggressively pursue counterfeit drug investigations with law enforcement partners in foreign countries as well as with federal, state, and local law enforcement here in the U.S.

The Honorable Bart Stupak

1. Mr. Stupak: "...I want to know about the 800 number. I mean, when something happens, people don't know who to turn to, how to report an adverse event. You rely upon those adverse events to see if there is a signal out there, whether there is a problem with the drug." (Transcript, P. 126).

The proposed rule on Toll-Free Number for Reporting Adverse Events on Labeling for Human Drug Products published on April 22, 2004, with the comment period ending July 21, 2004. In the proposed rule, FDA solicited comments on the wording of the proposed labeling statements. We received a number of comments suggesting changes to the specific wording of the proposed statements. We have been conducting studies designed to resolve issues raised by the comments and to optimize consumer understanding of the labeling statements. We plan to finalize the rule upon completion of these studies.

Please let us know if you have any additional questions.

Sincerely

Stephen R. Mason
Acting Assistant Commissioner
for Legislation

Enclosures