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 SEVENTH CONGRESS

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CONTENTS

	Page
Testimony of:	
Crawford, Hon. Lester M., Deputy Commissioner, Food and Drug Administration; accompanied by Janet Woodcock, Director, Center for Drug Evaluation and Research; and Catherine Zoon, Director, Biologics Evaluation and Research	30
Franson, Timothy R., Vice President of Clinical Research and Regulatory Affairs, U.S. Eli Lilly Research Laboratories	52
Pendergast, Mary K., Executive Vice President, Elan Corporation	60
Wood, Alastair J.J., Assistant Vice Chancellor for Research, Vanderbilt University School of Medicine	57
Material submitted for the record by:	
Food and Drug Administration, responses for the record	78

REAUTHORIZATION OF THE PRESCRIPTION DRUG USER FEE ACT

WEDNESDAY, MARCH 6, 2002

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

The subcommittee met, pursuant to notice, at 10:09 a.m., in room 2322, Rayburn House Office Building, Hon. Michael Bilirakis (chairman) presiding.

Members present: Representatives Bilirakis, Deal, Burr, Ganske, Norwood, Bryant, Buyer, Pitts, Tauzin (ex officio), Brown, Waxman, Strickland, Barrett, Capps, Towns, Pallone, Eshoo, Stupak, Wynn, Green, and Dingell (ex officio).

Staff present: Brent DelMonte, majority counsel; Steve Tilton, health policy coordinator; Eugenia Edwards, legislative clerk; John Ford, minority staff counsel; and David Nelson, economist.

Mr. BILIRAKIS. I call this hearing to order. Good morning. I would like to thank all of our witnesses for being here today to discuss the reauthorization of the Prescription Drug User Fee Act, which we fondly refer to as PDUFA, another one of those beautiful acronyms that we come with up here.

I know that many of you have been working around the clock to develop a set of recommendations for the Congress to consider in our deliberations. I want you to know that we appreciate the work you have put in so far, and would like to thank you in advance for your cooperation with the committee and Congress as we move forward quickly and cleanly to reauthorize this important program.

PDUFA as we know was first enacted in 1992, and then reauthorized in 1997 as part of the Food and Drug Administration Modernization Act, FDAMA. It is completely fair to say that this program has been a tremendous success.

In 1992, when the program was created, innovative treatments were taking far too long to reach patients. Since the creation of PDUFA, patients have been able to access breakthrough therapies more quickly and to improve their lives immeasurably.

In fact, many new drugs are available to American patients first. PDUFA has been so successful because it is a partnership between the agency, the industry, and patients.

The PDUFA statute allows the agency to collect fees that it inturn uses to ensure timely review of drug products.

I think it is important to state that this program was not created to ensure approvals. I repeat, it was not created to ensure approvals. The FDA and Congress strongly believed that products should

only be approved by the agency when they proved to be safe and effective.

The payment of user fees in no way guarantees approval of a product. The fees are merely used to help the agency facilitate timely reviews. Today the FDA can use the fees to hire more reviewers, build its information technology capacity, and for other administrative issues that facilitate the drug and biologic review process.

The fees are not intended to replace the FDA's appropriations and therefore do not constitute a tax. Our subcommittee would like to reauthorize PDUFA cleanly, and quickly, and I might add clearly.

This hearing will help us gain more insight into an important component of PDUFA, which is the performance goals letter. The performance goals letter represents agreements between the FDA, industry, and Congress, and the letter outlines goals that the agency must meet, which help frame the basis to judge the user fee program success.

Congressional review of the goals letter is critical because we must be certain that these extra PDUFA funds are used in the most appropriate fashion. Some have asked why is it so important to reauthorize PDUFA.

One reason that we need to move quickly and cleanly is that the agency by law cannot collect user fees unless Congress reauthorizes PDUFA. In effect, this means that the FDA would be forced to eliminate a large portion of its work force.

This would have devastating consequences for the prospects of continuing to ensure timely access to life saving products for patients. I know that none of us want to adversely effect patients' ability to access new life saving products. I believe that it would be more efficient for Congress to quickly enact the PDUFA reauthorization, and if we do so in as clean a manner as possible.

There are many issues that impact patient's access to new drug products. There is no question about that. Last week, we held a hearing on the uninsured, and we are continuing to work on solutions for that problem. Obviously, another issue that is at the top of my agenda, and this committee's agenda, and the President's agenda, is prescription drug coverage for our Nation's elderly.

I know that our committee will be working diligently to address many of these issues. I assure you that we will. We already are.

However, I would argue that PDUFA reauthorization is separate and apart from these issues. I think it is incumbent upon our committee to examine each of these issues thoroughly, and I am committed to doing so as soon as possible, and I have made a commitment to Mr. Brown in some of these areas.

I know that many members of other areas have concern with the FDA, and again I believe that our committee will examine these issues as needed. Reauthorizing PDUFA is vitally important to patients.

We sometimes fail to reauthorize in a timely fashion up here, but they are certain types of programs that are appropriated money, and they continue. NIH is in that category, and so many others.

PDUFA obviously as you know is in a different situation. We have got to ensure quick, clean, reauthorization of it. Our actions

will guarantee patient's continued access to innovative drugs, and meet our country's gold standards of safety and efficacy.

Again, I thank our witnesses for being here today, and I look forward to their testimony, and now I yield to Mr. Brown.

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

PREPARED STATEMENT OF HON. MICHAEL BILIRAKIS, CHAIRMAN, SUBCOMMITTEE ON HEALTH

Good morning, I now call this hearing to order. I would like to thank all of our witnesses for being here today to discuss reauthorization of the Prescription Drug User Fee Act (PDUFA). I know that many of you have been working around the clock to develop a set of recommendations for the Congress to consider in our deliberations. I appreciate the work you all have put in so far, and I would like to thank you in advance for your cooperation with the Committee and Congress as we move forward to quickly and cleanly reauthorize this important program.

PDUFA was first enacted in 1992 and then reauthorized in 1997 as part of the Food and Drug Administration Modernization Act (FDAMA). It is completely fair to say that this program has been a tremendous success. In 1992, when the program was created innovative treatments were taking far too long to reach patients. Since the creation of PDUFA, patients have been able to access breakthrough therapies more quickly and improve their lives immeasurably. In fact, many new drugs are available to American patients first.

PDUFA has been so successful because it is a partnership between the agency, the industry and patients. The PDUFA statute allows the agency to collect fees that it in turn uses to ensure timely review of drug products. I think it is important to state that this program was not created to ensure approvals. The FDA and Congress strongly believe that products should only be approved by the agency when they prove to be *safe and effective.* The payment of user fees in no way guarantees approval of a product. The fees are merely used to help the agency facilitate timely reviews. Today, FDA can use the fees to hire more reviewers, build its information technology capacity, and for other administrative issues that facilitate the drug and biologic review process. The fees are not intended to replace the FDA's appropriations, and therefore do not constitute a tax.

Our Subcommittee would like to reauthorize PDUFA cleanly and quickly. This hearing will help us gain more insight into an important component of PDUFA, the performance goals letter. The performance goals letter represents agreements between the FDA, industry and Congress. The letter outlines goals that the agency must meet, which help frame the basis to judge the user fee programs success. Congressional review of the goals letter is critical because we must be certain that these extra PDUFA funds are used in the most appropriate fashion.

Some have asked why is it so important to reauthorize PDUFA? One reason that we need to move quickly and cleanly is that the agency by law cannot collect user fees unless Congress reauthorizes PDUFA. In effect, this means that the FDA would be forced to eliminate a large portion of its workforce. This would have devastating consequences for the prospects of continuing to ensure timely access to life saving products for patients. I know that none of us want to adversely affect patients" ability to access new life saving products. I believe that it will be more efficient for Congress to quickly enact PDUFA reauthorization if we do so in as clean a manner as possible.

There are many issues that impact patients' access to new drug products. Last week, we held a hearing on the uninsured and we are continuing to work on solutions to that problem. Obviously, another issue that is at the top of my agenda, the Committee's and the President's is prescription drug coverage for our Nation's elderly. I know that our Committee will be working diligently to address many of these issues. However, I would argue that PDUFA reauthorization is separate and apart from these issues. I think that it is incumbent upon our Committee to examine each of these issues thoroughly, and I am committed to doing so as soon as possible. I know that many Members have other areas of concern with the FDA. Again, I believe our Committee will examine these issues as needed.

Reauthorizing PDUFA is vitally important to patients. It is incumbent upon us in Congress to ensure a quick, clean reauthorization of this legislation. Our actions will guarantee patients continued access to innovative drugs that meet our country's gold standards of safety and efficacy. Again, I thank our witnesses for being here today and look forward to their testimony.

Mr. BROWN. Thank you, Mr. Chairman. I want to raise two sets of issues this morning, and I would be remiss if I did not raise both sets of these issues. One set is specific to PDUFA.

We need to make sure that the legislation and related agreements strike the proper balance between speedier drug approvals and drug safety, the main charge of the Food and Drug Administration safety.

We need to evaluate whether FDA is overreaching in its performance goals, and ensure that the agency is devoting sufficient resources to pre-and-post market safety activities. We also need to make sure that this law strikes the proper balance between speedier drug approvals and drug efficacy.

We need to be sure that the drug companies are completing all the clinical studies they commit to. Absent complete data and proper drug labeling, faster drug approvals could simply hasten improper use, or inappropriate substitution of new drugs for existing ones. No one here wants that.

We need to make sure that the trigger mechanism in the bill isn't doing more harm than good. FDA's Center for Drug Evaluation should not have to starve critical functions, like the review of generic drug applications, and the review of direct to consumer advertising, and ongoing drug surveillance in order to meet the PDUFA spending trigger.

The fact that the President' budget happens to increase funding for some of these functions is no guarantee that future budgets will do the same. The other set of issues that I want to raise this morning is right before our eyes, yet we look past these issues when it is time to hold hearings, and time to write legislation.

There are pressing concerns for consumers for businesses, for other third-party payers in both the public and the private sector. Yet, we never seem to get around to addressing them.

I am referring to prescription drug pricing and prescription drug advertising, to prescription drug inflation. The three are related with the peculiar synergism to them, and they are a lethal combination for a U.S. health care system.

Mr. Chairman, I don't doubt the benefits of PDUFA. You and I have always worked well together and I don't doubt your interest in seeing patients continuing to have timely access to new medications.

But what I can't overlook are the drug issues that this Congress and this committee do not address, the ones we appear to be afraid to take on. With all due respect to this committee and this Congress, and especially its Republican leadership, jump when the drug industry says jump, and whether it is pediatric exclusivity, whether it is PDUFA, whether it is a whole host of issues.

It rushes to past registration when the drug industry wants us to pass legislation. We don't challenge drug industry pricing prices, even though these companies charge Americans 2, and 3, and 4, and in a few cases 10 times what they charge people in other wealthy industrialized countries for the same prescription drugs even though our taxes pay nearly half of the drug industry's R&D costs.

And even though the industry itself gets more tax breaks than any other major industry. Yet, we on this committee, and we in

this Congress, Republican leadership, refuses to address the issue of pricing.

The drug industry knows that not only do U.S. consumers pay more than consumers in other countries for the same medicines, we are also the only industrialized country that doesn't guarantee access to health care.

This industry knows that 70 million Americans, many of them seniors, have no coverage for drugs. The uninsured have the distinction of paying the highest prices in the world with no insurance for their medicines.

We don't take the pricing issue seriously, even though I bet that every member on this committee, Republican and Democrat alike, has spoken to seniors living on a social security check that increased 3.5 percent last year, but are paying for drugs that jumped 10 percent during that period, drugs that cost hundreds of dollars per prescription.

I sponsor regular bus trips to Canada, and the seniors on those trips are literally—save literally thousands of dollars in some cases on their prescription medicines, money that can buy food, money that can pay for heat, and other necessities.

We don't talk about that in this institution. When the drug industry wants us to move quickly to ensure that FDA doesn't hold their products up from getting to the market, we move with lighting speed to do their bidding.

Spiraling prescription drug costs are what is preventing Congress from adding a drug benefit to Medicare. We had better not talk about drug pricing or the impact of direct to consumer advertising on the Health Care Utilization Bill. Those topics seem to be taboo.

The European Union doesn't permit direct to consumer advertising, and Japan, Canada, Israel, don't permit direct to consumer advertising. Only one other country in the world, New Zealand, besides us, does allow it.

That is because direct to consumer advertising skews health care costs toward the newest, the most expensive drugs, regardless of whether these drugs are actually the best alternative for patients, regardless of the impact on American's health care bill.

The drug industry claims that it is doing consumers a favor. The DTC advertising is a breakthrough in consumer education. In 2000, last year, or 2 years ago, the drug industry advertised 1 percent of the newly 10,000 prescription drugs available to consumers.

And 95 percent of all DTC advertising was spent on 50 drugs, .5 percent of the 10,000 drugs on the market. The drug industry claims that its advertising is highly educational. DTC advertising is more highly profitable than it is highly educational. But we don't talk about that here.

Mr. Chairman, I will continue to work with you on a bipartisan basis on the Prescription Drug User Fee Act. I will work with you to ensure that we bring the best possible bill to the floor.

But I hope that this committee and this Congress will not continue to limit our focus to those issues that the drug industry wants us to consider. Our complacency already is taking far too great a toll on our constituents. Thank you.

Mr. BILIRAKIS. I thank the gentleman. With all due respect, I would suggest that probably the patients out there also would like to see us streamline this process, and the Chair now would yield to the chairman of the full committee, Mr. Tauzin.

Chairman TAUZIN. Thank you, Mr. Chairman. Let me commend you for holding this hearing, and I look forward to working with you and the rest of the subcommittee in ensuring that the Prescription Drug User Fee Act or PDUFA is reauthorized cleanly and quickly.

I would further like to congratulate the FDA and the industry for completing their negotiations on the performance side agreements which must accompany this legislation. As you know that was a predicate to our moving and I want to thank all of you for moving as quickly as you did.

I look forward now to learning more about the substance of those agreements. I think it is import to start by noting certain facts which will guide the committee's consideration of PDUFA.

The first is that the Act has worked extraordinarily well. Since the Act was first passed in 1992, drug review times have decreased dramatically, and the rate of drug withdrawal has remained constant.

Now, you can only conclude one thing from that. That means that necessary drugs are reaching patients who need them much more quickly without drugs being approved that have to be withdrawn at any greater rate than before.

That is a great success story. Not for drug companies, but for patients in America, who need these drugs to sustain their lives, and prevent illness, or to protect against damaging ravages of those illnesses.

Now, half of all new drugs are first made available in the United States; and 80 percent of all of the new drugs are available to American patients within a year of the first approval.

In short, PDUFA is working, and it must be renewed, and if we fail to renew it, we will have failed American patients across this country.

Second, if the Act is not authorized by the end of this fiscal year, there are no carryover balances which would allow the FDA to continue to pay the reviewers that are funded by PDUFA.

This means that these reviewers will have to be laid off if we do not reauthorize this bill, and the layoffs could come in the middle of this year. We know it. If we don't complete our work on this bill prior to August the FDA will begin the process of notifying employees that their positions may be eliminated.

I think this should not be allowed to occur as it would be harmful not only to the employees and their morale, and the work that they do in reviewing drugs, but again to the patients of America that would depend upon these reviews.

Last, the committee and Congress have a very aggressive health agenda this year. We have promised the House leadership, and the House, working together with Ways and Means, that we are going to produce a Medicare Reform and Drug Benefit Act by late April to early June.

If we are going to get that work done, we have to complete this work on PDUFA very quickly. And because of these factors, I be-

lieve it is essential that the committee produced a clean reauthorization this year.

I do not deny that there are other FDA reforms that frankly I would like to see enacted this year. For example, I am very interested in the Greenwood-Eshoo Device Reform Bill, as well as some of the other reforms.

Mr. Burr has one of them, in that I am very interested, and some of which may not sit very well with my friends on the Democratic side of our committee. And I know that there are FDA reforms that some on the other side may wish to add to this bill that may not sit well with members of this side.

But if we weigh this bill down with those kinds of debates, if we continue to fight old battles over issues in which everybody had a fair chance to debate them and offer amendments on the floor, and if we continue to fight those old battles and add new battles to this issue, we just won't get our job done, and this committee will have failed America's patients.

My message is that this is not the vehicle for consideration of all of these matters. We can't allow this reauthorization to be turned into some kind of a Christmas tree.

If we do this, we increase the likelihood that the hardworking FDA employees, critical to American patients, will be presented with RIF notices later this summer, and we can't let that happen.

So let's deal with PDUFA now, and then turn our attention to the other FDA reforms. It is my every intent to see the committee consider these other FDA matters later in this session, if the members will continue to cooperate as they have done so willingly in a bipartisan fashion to keep on our schedule.

And I intend to work with the chairman of this committee, and you, Mr. Brown, to see to it that those issues are addressed in good order, and I yield back the balance of my time.

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

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

Mr. Chairman: I commend you for holding this hearing, and look forward to working with you and the rest of the Subcommittee in ensuring that the Prescription Drug User Fee Act, or PDUFA, is reauthorized cleanly and quickly. Further, I'd like to congratulate both the FDA and industry for completing their negotiations on the side agreements which will accompany the legislation, and I look forward to learning more about the substance of the agreement.

I think it's important to start by noting certain facts which will guide the Committee's consideration of PDUFA. One, PDUFA has worked very well. Since the Act was first passed in 1992, drug review times have decreased markedly, and the rate of drug withdrawal has remained constant. Roughly half of all new drugs are first made available in the United States, and 80% of all new drugs are available to American patients within a year of first approval. In short, PDUFA is working and must be renewed.

Second, if the Act is not reauthorized by the end of this Fiscal Year, there are no carry-over balances which will allow the FDA to continue to pay the reviewers funded by PDUFA. This means that these reviewers will have to be laid off if we do not reauthorize the bill this year. Further, if we do not complete work on this bill prior to August, the FDA will begin the process of notifying employees that their positions may be eliminated. I think this should not be allowed to occur as it would be so harmful to employee morale.

Last, the Committee and the Congress have a very aggressive health care agenda this year. Because this Committee is going to dedicate so much time to creating a Medicare prescription drug benefit and enacting structural Medicare reforms, it is absolutely essential that the Committee address PDUFA reauthorization now.

Because of these factors, I believe it is essential that the Committee produce a clean reauthorization this year. I do not deny that there are other FDA reforms I would like to see enacted this year. For example, I am very interested in the Greenwood/Eshoo device reform bill, as well some other reforms which may not sit well with those on the Democrat side. And I know that there are FDA reforms that some on the other side may have which would not sit well with me.

My message to all is that this is not the vehicle for consideration of those matters. We cannot allow reauthorization of PDUFA to be turned into a Christmas tree. If we do this, we increase the likelihood that hard-working FDA employees will be presented with RIF notices later this summer. We cannot allow this to happen. Let's deal with PDUFA now, and then turn our attention to other FDA reforms. It is my every intent to see the Committee consider other FDA matters later in this Session, so let's produce a clean PDUFA reauthorization now.

Mr. BILIRAKIS. Thank you. The Chair yields to Mr. Dingell.

Mr. DINGELL. Mr. Chairman, I thank you, and I commend you for scheduling this hearing today. We will soon be considering for the third time legislation to provide user fees for prescription drug approvals.

I have supported these user fees from the beginning, and will continue to do so. I would like to tell a little bit about the history of this. The Subcommittee on Oversight and Investigations of this committee conducted a series of investigations on behavior at Food and Drug with regard to a major part of the pharmaceutical industry, namely the generic drug industry.

We found massive scandal there. We found serious misbehavior in the Agency, picking and choosing, and making judgments on who would be considered. Because the docket of the Agency was clogged, and because there were not enough people, and the people were not properly paid to do the kind of work that was necessary to see to it that the business of the agency was conducted speedily and that the concerns of persons and corporations interested in new drug applications was handled speedily, well efficiently, and honestly. The result of these investigations were several things.

First, there were a lot of people who went to jail as they very well should. Second of all, there were a number of changes in the administrative procedures at the agency. Third of all, the agency found as everybody knew that it needed to beef up its business, because it was proceeding far too slowly in terms of making the necessary clearance.

The industry was waiting 7 to 10 years and more for a new application to be cleared. There is only one way that we can address the root of these problems, and that was to see that a sufficient number of properly paid and adequate in number employees at Food and Drug would address these problems.

The industry understood it, and the committee understood it, and the Congress understood it, and we passed PDUFA as a result thereof.

The result of this was that we got good people to do the work that needed to be done. The Food and Drug Administration cleaned up its act, and as I said a number of deserving people did go to jail.

The result was that industry, because of the user fees that were imposed, and to which they agreed, and to which they supported, made it possible for FDA to hire enough people from essentially a dedicated fund to provide the services that the industry needed.

The result was that the consumer benefited. The industry has been happy, and the industry has honored its commitments, and the Food and Drug has provided excellent service in these matters. The review time has speeded up, and industry is able to get its new drug applications more speedily processed.

The result has been everybody has profited. The result has been that this committee has defended these user fees, and has not allowed the budgeteers who in their enthusiasm of run around and grab any loose nickel in the government till to apply to some purpose that they happen to believe is in the public interest, has not been able to prevail.

It is time for this legislation to be extended because to go back to the situation that it was before would be intolerable from the standpoint of everybody; the industry, the committee, the Congress, FDA, the consuming public, which is dependent upon getting these drugs speedily and thoroughly, and carefully, and honestly processed.

And of course the business and the economic activity, and not just of the pharmaceutical houses, but of the United States. This is a good piece of legislation and it should move rapidly, and I hope that my colleagues are keeping in mind the history of this and will understand why it is necessary for us to proceed speedily.

I ask therefore that the entirely of my statement be inserted in the record, and I urge the speedy, favorable, and friendly consideration to an important piece of legislation upon which everyone has agreed, and I thank you for your courtesy to me, Mr. Chairman.

[The prepared statement of Hon. John D. Dingell follows:]

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

Mr. Chairman, thank you for scheduling today's hearing. Soon we will consider for the third time legislation to provide user fees for prescription drug approvals. I have supported user fees from the beginning, and continue to do so. I will repeat here what I said on the floor of the House in November 1997 when we passed the current user fee: "These user fees, and FDA's own commitment to excellence, help make this agency the finest of its kind in the world."

But this program can be improved. I join my colleagues, Representatives Stupak and Brown, in their desire to improve the current program's post market safety features. More drugs than ever are first launched in the United States. Modern marketing and advertising practices result in more consumers using more drugs in a shorter period of time after FDA approval than ever before. Our population is more diverse than ever. Diseases and drug therapies to treat them present new challenges. These factors argue in favor of an enhanced post market surveillance system that tracks drugs after they have been approved so that we know drugs are safe and effective in the real world and not just at the moment they leave FDA's door after clinical trials. I know that we will hear encouraging testimony about improvement in this area. The legislative text, plus any related side agreements, will need to implement safety improvements.

Also, concerns have been raised about PDUFA's role in the drug review process, so I look forward to today's testimony on these as well. Mr. Chairman, I ask unanimous consent to have included in the record the Patient and Consumer Coalition's PDUFA paper, which outlines many of these concerns. This coalition includes many consumer advocates, patient groups, including the International Union, UAW. I further request that Dr. Crawford review this paper and provide us with a response or comment to the points and concerns raised in that document.

Finally, I want to echo the request of our Ranking Member, Mr. Brown, that this Subcommittee consider drug price and access issues this year. While I support the effort to produce a bipartisan PDUFA bill, we all know that there is a great deal of interest in these other issues, and we must begin to address them.

Mr. BILIRAKIS. We are going to try to continue on here, and I am not sure that we will be able to do it. Dr. Ganske, the Chair exercises its preoperative under the rules to limit additional opening statements to 3 minutes. Dr. Ganske.

Mr. GANSKE. Thank you, Mr. Chairman, and I will be much briefer than that. I share the concerns of you and Chairman Tauzin. There come sometimes in Congress where you need to agree on what you can agree on, and move on with contentious issues in other forums.

This is a very important bill, and you can see from the data that has been gathered that the approval times have been reduced by more than half in many instances. I think that is a testimony that, as Chairman Tauzin has pointed out, we have not seen an increase in drug withdrawals we were dealing with when PDUFA was first passed. There was a general consensus, a bipartisan consensus, that it was just taking too long, and we needed to streamline the process, and maintain safety standards, but try to help to get this process moving because lives were at stake.

Patients needed their drugs, and it has been making a difference in their health and maybe even in staying alive. And delays were causing people their health and their lives.

So let's move to a resolution on this in an expeditious manner. I look forward to reviewing the testimony by the people on the panels today, and thank you for coming.

Mr. BILIRAKIS. Thank you, Dr. Ganske.

Mr. Waxman.

Mr. WAXMAN. Thank you very much, Mr. Chairman. The Prescription Drug User Fee Act has achieved its primary goal to speed the review of new drugs in the U.S. New drugs are now available in the U.S. faster than anywhere else in the world.

This is an important achievement, and we should make every effort to ensure that people have access to safe and effective new medicines as quickly as possible. This achievement, however, has come at a cost. That cost is an under-funded drug review staff working on too many drugs, and too little time.

Even the FDA has called the working environment there a sweat shop; hours are long, and salaries and training opportunities are poor, and turnover is high.

Speeding drug approvals has had another cost as well. It has siphoned off essential funds for post-market safety programs, for review of direct to consumer ads, and for generic drug approvals.

All of these FDA programs are critical to ensuring that drugs are safe, and affordable, and all are severely under-funded. Most importantly, the cost of faster approvals has been a loss of public confidence in the safety of new drugs.

And as this has been happening, we have witnessed a large increase in direct to consumer advertising of prescription drugs, ads that were not permitted at the time that PDUFA was first enacted.

It has been demonstrated that these ads are extremely successful at fueling both demand by consumers and prescribing by physicians. What is so troubling is that many of these ads are often misleading and unbalanced.

We should have a system that ensures that direct to consumer drug ads are adequate and fair. The FDA has only 13 staff to review over 37,000 pieces of prescription drug advertising each year.

Speeding the review of new drugs is important, but ensuring the public that drugs are safe and effective demands more, and we cannot sacrifice safety for speed. User fees paid by the pharmaceutical companies have provided the means to turn a slow approval process into one of the fastest in the world.

It could provide the means to build a program that provides assurance to the public that new drugs are safe and effective, and that the advertising is truthful. Until now the pharmaceutical industry has resisted paying user fees for any purpose other than speeding approvals.

I understand that this agreement that has been worked out with the FDA would have some of the user fees go to a post-market, as well as a premarket review of drugs. I applaud this beginning, but much more is needed. In closing, let me note that today's hearing covers only one of the prescription drug issues confronting us.

The most critical of these is the high price of prescription drugs causing hardship to the poor, and to our seniors, and to driving up the cost of health care for all of us. And adding to the crisis in affordability, we know that there have been serious abuses of the Hatch-Waxman law by brand-name manufacturers trying to keep generic drugs off the market. We owe it to the public that this committee address these issues as well, and I look forward to working with my colleagues on the committee to solve thee pressing problems.

And I hope that we can do so in a fair and bipartisan manner, and be sure that we consider all of these issues as carefully as possible. Thank you.

[The prepared statement of Hon. Henry A. Waxman follows:]

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

The Prescription Drug User Fee Act has achieved its primary goal—to speed the review of new drugs in the US. New drugs are now available in the US as fast or faster than anywhere else in the world. This is an important achievement. We *should* make every effort to ensure that people have access to safe and effective new medicines as quickly as possible.

This achievement has come at a cost, however.

That cost is an underfunded drug review staff working on too many drugs in too little time. Even FDA has called the working environment there a "sweatshop." Hours are long, salaries and training opportunities are poor, and turn-over is high. Under those conditions, it is difficult to have complete confidence in the approval decisions they reach.

Speeding drug approvals has had another cost as well. It has siphoned off essential funds for post-market safety programs, for review of direct-to-consumer ads, and for generic drug approvals. All of these FDA programs are critical to ensuring that drugs are safe and affordable, and all are severely underfunded.

Most importantly, the cost of faster approvals has been a loss of public confidence in the safety of new drugs.

As this has been happening, we have witnessed a large increase in direct-to-consumer advertising of prescription drugs—ads that were not permitted at the time PDUFA was first enacted. It has been demonstrated that these ads are extremely successful at fueling both demand by consumers and prescribing by physicians.

At the same time, many believe that these ads are often misleading and unbalanced. Whatever your view of whether these ads should be allowed (and frankly I don't believe they should), most of us would agree that we should have a system that ensures that direct-to-consumer drug ads are accurate and fair. We do not have

such a system. Right now, FDA has only 13 staff to review over 37,000 pieces of prescription drug advertising each year.

Speeding the review of new drugs is important. But ensuring the public that drugs are safe and effective demands more. We cannot sacrifice safety for speed. And we must be vigilant in our oversight of prescription drug ads to be sure that misleading ads do not prompt unsafe or inappropriate use of drugs.

User fees paid by the pharmaceutical company have provided the means to turn a slow approval process into one of the fastest in the world. And they could provide the means to build a program that provides assurance to the public that new drugs are safe and effective, and that their advertising is truthful.

Until now, the pharmaceutical industry has resisted paying user fees for any purpose other than speeding approvals.

They have fought proposals to use their fees to ensure that the safety and effectiveness of their drugs is monitored and validated after approval.

They have been unwilling to allow their fees to be used to ensure that their advertising is fair and truthful.

I believe that the industry has been short-sighted. It is in the interest of manufacturers to support programs that give Americans confidence that prescription drugs can be safely used as advertised.

This week we learned that the industry has agreed to pay increased fees to adequately fund the premarket review of drugs and a small amount to support a postmarket safety program. I applaud this beginning. But much more is needed.

Right now, the pharmaceutical industry spends one tenth of one percent of its revenues on user fees. Meanwhile, faster approvals have saved the industry billions of dollars per year. I don't think it's too much to ask that the industry pay what is necessary to ensure the safety and effectiveness of their drugs before and after approval. I don't think it's too much to ask that the industry help FDA ensure that direct-to-consumer ads are accurate and balanced. Continued public confidence in prescription drugs is in the balance.

While I have concerns about some of the details of this reauthorization, I believe that good progress is being made and I look forward to working with my colleagues on both sides of the aisle on this important legislation.

In closing, let me note that today's hearing covers only one of the prescription drug issues confronting us. The most critical of these is the high price of prescription drugs—causing hardship to the poor and to our seniors and driving up the cost of health care for all of us. Adding to the crisis in affordability, we know that there have been serious abuses of the Waxman-Hatch Amendments by brand-name manufacturers trying to keep generic drugs off the market. We owe it to the public that this Committee address these issues. I look forward to working with my colleagues on the Committee to solve these pressing problems.

Mr. BILIRAKIS. I thank the gentleman. Mr. Bryant.

Mr. BRYANT. I thank the chairman, and I will be brief in light of the pending vote, as well as the need to begin to hear our outstanding panels of witnesses.

And I simply will echo and adopt those statements of my colleagues on either side of the aisle that are in support of moving this bill expeditiously, and in an unencumbered fashion, and not getting into these contentious issues that seem to always crop up that are legitimate in some ways, because they are contentious.

But there are certainly different sides to the issue that need to be fully aired at some point in the future. The issue today is this bill, and we need to move it quickly. Second, and I will close by recognizing my happiness in having a Tennessee doctor here today testifying from Vanderbilt, Dr. Wood, who will be on the second panel.

And I welcome him, especially as I do all the other witnesses, and look forward to his testimony. Many of us are in other committees, and I have another committee marking up a bill which requires votes, and so I will be in and out of this hearing.

But, Mr. Chairman, thank you for having it nonetheless, and I yield back my time.

Mr. BILIRAKIS. I thank the gentleman, and I think it is only fair that we give everyone who wants to make an opening statement a fair opportunity to do so. I am afraid in wanting to go and vote that you are liable to miss out.

Dr. Norwood is coming back to sort of take over, but I would like to think that we would hold it open, the opening statement period. Let's see. Mr. Pallone for an opening statement.

Mr. PALLONE. Thank you. Thank you, Mr. Chairman. I will try to be brief. I just wanted to say that I think it is sort of a no-brainer that we are going to reauthorize PDUFA before its sun sets, and I obviously agree with that.

But I just wanted to reiterate what some of my Democratic colleagues have said, is that we know that this is coming up, and this is another bill that the brand name pharmaceutical industry supports, but we don't get the attention focused on some of the other issues that we consider important.

I have to say that I was at—you know, I went and bought a prescription for my cat. I guess it was Monday night. Today is Tuesday or Wednesday, as I forget, but when we were back in the District and I was waiting in line as the pharmacy in my hometown and everybody at the counter was considered about the pricing issue.

You know, how much they were paying, and how the prices were going up, and then I bought the prescription for the cat, which was probably the lowest prescription that was being sold at that counter that evening.

And it is so amazing to think—you know, because we talk about this as sort of a joke, but the fact of the matter was that I was paying less for the cat than most of the people at the counter were paying for the prescription drugs that they had to buy for themselves for human beings.

And when you talk about the pricing issue, it just seems that our Republican colleagues are reluctant to bring it up. Even the President, over the week, he rolled out this drug card again, and he is talking about the drug card and how that is going to do all these wonders.

And everybody in my district tells me that the drug card—you know, they already have it, and maybe they will get a 10 or 15 percent reduction, but they already have it. And so why is this Administration promoting that, rather than dealing with the pricing issue.

But of more immediate concern when you talk about PDUFA is my concern that PDUFA in fact underscores the need for generic drugs to enter the market. As resources within the FDA are allocated to approving drugs in accordance to user fees, it has been reported that limited FDA resources are taken away from other important areas within the agency, particularly an area within the FDA that are responsible for evaluating and approving generic drugs.

And I really think that generics in many ways are the keys of trying to reduce prices. We need statutory and legislative initiatives that allow timely access to availability of generic drugs.

However, today we are preparing to reauthorize legislation that guarantees timely approval of brand name drugs, while leaving behind necessary generics from potentially entering the market.

So once again it is not just a question of what we roll out and what bills we deal with first, which clearly favors the brand names and not these other issues. But it is also the fact that even this legislation I think short changes generics, which I think is a major issue that we want to deal with if we are going to deal with the pricing issues.

So I am concerned, and I know that the time is short, but I am not concerned that although this bill needs to be reauthorized, and we are here to do it, let's get to some of these other issues.

Let's not shortchange generics and let's deal with the pricing issues, and at least have some hearings on it. Thank you, Mr. Chairman.

Mr. BILIRAKIS. We have 5 minutes before the vote is up. All right. When Dr. Norwood returns, he will just have to wait until we return. We are in recess.

[Brief recess.]

Mr. BILIRAKIS. Shall we continue?

Dr. Norwood.

Mr. NORWOOD. Thank you, Mr. Chairman, and especially thank you for holding this hearing. It is very timely and very appropriate for us to consider PDUFA reauthorization.

And in the interest of getting to our witnesses, I will be uncharacteristically brief. Mr. Chairman, PDUFA has worked. It's just of that simple. It is a program that is getting new drugs to Americans who need them, and it is getting those drugs to Americans far faster than before we passed PDUFA in 1992, and in a safe manner.

We are approving drugs much faster, but yet drug safety doesn't seem to have been compromised. And I am very heartened by the work that the FDA is doing to improve on the original model, and I am looking forward to their comments on their efforts to date.

However, Mr. Chairman, I have serious concerns about the cost and pricing of drugs, and I have some strong opinions about areas that I think we need to give oversight to FDA.

But I want to point out that I am not going to press any of those things as part of a conversation with PDUFA because I agree with you and Chairman Tauzin that we need to have a very clean reauthorization bill, and do it sooner rather than later.

It doesn't need to have things tacked on it that are controversial, and so I support you 100 percent. But I do hope as the chairman said that we will return to the subject of drug costs later this year, and give us all an opportunity to discuss that and look at that very closely.

I would like to encourage frankly my colleagues on this committee to do the same, and let's get this reauthorized because it is the right thing to do for the American patient, and then let's have our discussions that we need to have. Thank you, Mr. Chairman.

Mr. BILIRAKIS. I thank the chairman. Mr. Stupak.

Mr. STUPAK. Thank you, Mr. Chairman, and with 3 minutes, let me get right to the gist of my opening statement. We have heard

a lot about how PDUFA works, but at what cost? What have we sacrificed?

What we have sacrificed under PDUFA is honesty, accuracy, and informative labels. These are the duties and responsibilities that affect every American consumer. Therefore, we must be very careful to make sure that we do not compromise safety or effectiveness that the American public has come to expect.

Now, I have heard a lot about this tentative agreement, and we don't know what it is because it is not in writing. It is verbal. Now we were briefed yesterday by FDA officials, and here are some of my concerns from that briefing.

First of all, the FDA is financially dependent upon an industry that it regulates, and because under the new agreement user fees are dramatically increased, dependence will grow dramatically.

Instead of using industry funds, Congress should appropriate enough money to ensure FDA's regulatory authority is completely independent, above approach, and free of undue pressure from the drug industry.

Second, it is more than clear that the approval of the drug or device based on a relatively short term information does not always give us complete information about a drug.

The number of drugs pulled off the market in the last 4 years is 12.

Now, I agree that three were pre-PDUFA, but nine drugs that raced through an accelerated PDUFA approval process with incomplete information brings me to my third point, Phase IV studies, also known as post-marking surveillance, are nightmarishly inadequate, and neglected to a shameful extent by both the FDA and drug manufacturers.

In 1997, we did PDUFA-2, and we ordered a study from the FDA that would summarize how well the industry complied over the past 5 years with mandates to do Phase IV studies.

This report, which was due to Congress by October 1, has been sitting in the Office of the Secretary of Health and Human Services, even though by law we are supposed to receive it 5 months ago so we can do PDUFA reauthorization. Why the hold-up?

I believe the results of this study will show the vast majority of drug companies do not do their mandated post-marketing surveillance studies. According to some estimates, 90 percent of them were never completed. Ninety percent. So how do we enforce it?

I understand that PDUFA-3 as negotiated thus far comes a long way to address the major concerns with post-marketing surveillance, but without any enforcement, there will be no post-marketing surveillance as we see in PDUFA-2.

So I suggest that we put civil monetary penalties pegged to the sales of drugs as one option that we should consider.

Another area of concern is the ability of the drug manufacturers to game the system.

While waiting for requested and required information from the manufacturer, the FDA should be able to stop the clock on the time constraints that PDUFA imposes. Due to extremely tight deadlines in PDUFA, manufacturers know that they can delay their response to FDA's request for information long enough so that the FDA is

forced to make a decision without being able to do a thorough review, and double-check data.

We had one breast cancer drug, and the FDA got the information 1½ weeks before the PDUFA deadline would run.

My final concern is subpoena power. The FDA is one of the few health and safety regulatory agencies that does not have subpoena power.

Subpoena power would give the FDA the authority it needs to inspect manufacturers' documents in a timely fashion. This is one issue that we need to explore in this context.

And last, but not least, safety, adequate labeling, and compliance with Federal regulations always seem to fall by the wayside when we rush through PDUFA or whatever it might be.

We did pediatric exclusivity here recently, and we are still waiting for studies. While this committee may have defeated pediatric exclusivity, it is going to come back under PDUFA.

I recently wrote a letter to Bristol-Myers SQUIB last month about a drug called Serzone. Sixteen other members joined me. That was a drug that did a pediatric exclusivity in 1994. We are still waiting for the results of that study.

We have young people who have suffered liver damage from this drug, and we can't even get anyone to tell us what the results of that study was for pediatric exclusivity 6 years ago. That's ridiculous, and it has to stop.

We want to make sure that drugs are safe, and we want to make sure that we have adequate labeling, and we want to make sure that the FDA has adequate information. Therefore, Mr. Chairman, from subpoena power to enforcement power, the pediatric labeling under the pediatric exclusivity issue, these are all issues that must come up.

I know that you and the chairman have said don't cloud up this bill with other issues. Mr. Chairman, this is the only vehicle we will probably see this year. On this side of the aisle, some of us are going to work to make safety, accuracy, honesty, and labeling, is put back in to the Food and Drug Administration and the Cosmetic Act of this country.

Mr. BILIRAKIS. Mr. Pitts for an opening statement.

Mr. PITTS. Thank you, Mr. Chairman, for holding this important hearing today on PDUFA reauthorization. I look forward to hearing from our witnesses. Since I have got two hearings going on at the same time, I may miss some questioning.

I want to up-front mention my concern that the plasma industry be represented as the dialog on performance standards moves forward. As you may know the plasma industry provides unique life saving therapies, and also pays substantial user fees.

I learned just recently that the CBER director has agreed to meet with the plasma industry to discuss performance standards, and I am hopeful that these discussions are productive. Mr. Chairman, the new medicines approved by the FDA in recent years include innovative treatments for many life threatening diseases, and patients and their families will benefit from the industry's innovation and so will the health care system.

As we all know, recent research shows new medicines can help keep people out of the hospital and help them avoid costly surgery and other treatments.

Mr. Chairman, while we may have many ineffective programs in our Federal Government that some would like to see expire, PDUFA is certainly not one of them. Our committee should act as quickly as possible to reauthorize this act, and I yield back the balance of my time. Thank you.

[The prepared statement of Hon. Joseph R. Pitts follows:

PREPARED STATEMENT OF JOSEPH R. PITTS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF PENNSYLVANIA

Thank you, Mr. Chairman for holding this important hearing today on the Reauthorization of the Prescription Drug User Fee Act.

I look forward to hearing from our witnesses today about whether the Act has met its purpose of speeding the review of drugs and biologics without compromising patient safety.

From my preliminary reading, it is clear that PDUFA has decreased the review time for drugs and biologics.

It is gratifying to see the positive results of PDUFA that occurred almost immediately after passage. The fact that the review time for standard drug applications has been reduced from 26.9 months in 1993 to less than 12 months in 2001 is great progress.

Mr. Chairman, since we all share the goal of getting life-saving drugs to patients as quickly as possible, I am hopeful that we can reauthorize this important Act as soon as possible.

I hope that this committee can finish our business on this by August, 2002, so that the FDA does not have to begin the process of notifying PDUFA-funded employees that they may be laid off.

I am also interested hearing from our witnesses today about the recent agreement between FDA and industry on the goals they have developed that will pave the way for us to reauthorize PDUFA III.

Since I have another hearing right now in another committee, I may miss my chance to ask questions. Therefore, I want to mention my concern that the plasma industry be represented as the dialogue on performance standards moves forward. As you may know, the plasma industry provides unique life-saving therapies and also pays substantial user fees.

I learned just recently that the CBER Director of FDA has agreed to meet with the plasma industry to discuss this issue. I am pleased that this has been arranged and hopeful these discussions are productive.

Mr. Chairman, the new medicines and biologics approved by the FDA in recent years include innovative therapies for many life threatening diseases. Patients and their families will benefit from the industries' innovation, and so will the health care system. As you know, recent research shows these new treatments can help keep people out of the hospital and help them avoid costly surgery and extensive medical care.

Mr. Chairman, while we have many ineffective programs in our federal government that some of us would like to see expire, PDUFA is certainly not one of them. Our committee should act as quickly as possible to reauthorize this Act.

Mr. BILIRAKIS. Ms. Capps for an opening statement. Ms. Eshoo for an opening statement.

Ms. ESHOO. Thank you, Mr. Chairman, along with all of my colleagues from the committee for having this important hearing. I am very proud of the PDUFA program and how it has revolutionized the prescription drug approval process.

So reauthorizing this legislation is one of the most important things that I think our committee can do this year, and we must do it this year.

Prescription drugs and biologics are changing health care on a daily basis. I am constantly amazed by the science and what products have done to make our lives better. Twenty years ago, a pa-

tient with chronic diabetes could expect extended hospital stays, shorter life span, and higher health care costs.

Today, prescription drugs allow diabetics to manage their illness from the comfort of their own home, and they have expectations of a much fuller and better life. PDUFA has gone a long way toward ensuring the drugs to treat diabetes, and other illnesses, reach the patients that so desperately need them in a timely and responsive manner.

Prior to the initial passage of PDUFA, it often took years for drugs and biologics to be reviewed by the FDA. The agency was strapped for both financial and human resources, and was unable to devote enough time and energy to the review process.

And that's really where the rubber meets the road. It is the review process. In the 10 years since it was passed, PDUFA funding has revamped and revitalized the review process, and allowed the FDA to increase its staff and its expertise, and upgrade its IT systems, and better structure the management of the review process.

So clearly this is an example of legislation that has worked, and is working very well. So we have to seize this opportunity, and we need to reauthorize, and we need to do it in an expeditious manner.

The FDA and the drug biotech industries have been working closely to draft what is known as a side agreement that always accompanies PDUFA. I am glad that they have come to an initial consensus, and I look forward to reviewing the agreement soon.

I do want to take this opportunity to stress to the chairman and my colleagues the importance of reviewing this agreement before, and not after, but before we mark up the legislation.

Given that this agreement is not bound by statute, it is important that members be given ample time to review and have any concerns addressed by the stakeholders. We shouldn't let a desire for expeditious action overtake good, sound policymaking.

So, in closing, I would like to once again reiterate my support for PDUFA, the user fee program, and in hearing Chairman Tauzin make his opening statement, I, too, am proud of the work that we did in reauthorizing in 1997.

But we also have part of PDUFA, and I understand the complications of not joining them this time, because that is the chairman's view and wish, and I think that he obviously has very good reasons for it.

We are not going to issue with notices, but the reauthorization of FDAMA is a very, very important step for this committee and the Congress to take this year as well. As we talked about he reliance of patients across the country on prescription drugs, they are also increasingly reliant on the medical devices that not only give them hope, but bring them good and improved health day in and day out.

So I think that it is very important for the committee, and Mr. Chairman, for you, to start thinking about that, and that we have a hearing on the bill, and you know that I will work closely with you in order to accomplish that.

So thanks again for having this, and I look forward to the review of the side agreement and legislation moving so that we can get this done. It is good legislation, and it has worked well, and it has

served the American people well. That's the reason that we are all here. Thank you, Mr. Chairman.

Mr. BILIRAKIS. Thank you. Mr. Deal for an opening statement.

Mr. DEAL. Thank you, Mr. Chairman.

Just a couple of thoughts. I would like to thank Dr. Woodcock for your willingness to meet with me in the past on the issues that are related to your agency's functions.

And to Ms. Pendergast, to say that Elan Pharmaceutical, which is headquartered in my district, we are always pleased to have representation here. Certainly the issue is an important one, and one that many of us have looked forward to this hearing, and I thank the chairman for holding it.

Certainly the issues that will make the availability of drugs in a more responsive and quicker fashion is certainly something that I think all of our constituents want.

But at the same time the concerns voiced by many of my colleagues about safety are concerns that I think this hearing hopefully, and others, will reinforce to assure us that we have the best and safest products on the market. And with that, I yield back my time, Mr. Chairman.

Mr. BILIRAKIS. I thank the gentleman.

Ms. Capps for an opening statement.

Ms. CAPPS. Mr. Chairman, I appreciate the opportunity that you are giving the subcommittee to review the Prescription Drug User Fee Act. Prescription medications have radically changed health care, and improved the lives of millions of Americans.

They have become an essential component of what is now standard medical care, at least for those that can afford it. This committee has often struggled with issues relating to prescription drugs.

And whether we are talking about seniors on Medicare or pharmaceuticals for children, there are basically three questions that we asked when we address prescription drugs. How fast can a patient get them, and how safe and effective are they, and how much do they cost.

We want them to be quick to market, save to use, and affordable to patients. PDUFA has addressed the first matter by significantly improving FDA's ability to review and approve new medications.

These medications that are quicker to market seem to have helped many Americans enjoy a higher quality of life. That being said, PDUFA raises some questions about the issue of safety, and may contribute to some of our problems addressing cost.

In theory, while PDUFA accelerates the approval process for new drugs, these drugs still must be safe before they are approved, and there is some concern that the performance goals of PDUFA may end up putting drugs on the market before they are sufficiently tested and reviewed.

That is what we must examine.

Post-market surveillance is supposed to catch anything like this, but with the resources for these surveys, and FDA's authority to insist on them, are limited. This is certainly something that we need to correct as we move toward reauthorization of PDUFA.

I am also worried that PDUFA may help keep the cost of prescription drugs inflated. The fees themselves, of course, add the

cost to medications, but more importantly PDUFA also forces the FDA resources toward the approval of brand name drugs, denying those resources for the review of generic drugs.

Generics access to the market is given to lower the cost of prescription drugs dramatically, but the effect is limited because the FDA is so slow to approve them. In 2001, the average time it took to review and approve a new brand name drug was 12 months.

The FDA took nearly twice that long, 22 months on average, to approve generic drugs. I think this is appalling. And even when these generics are approved, it does not necessarily mean that they are going to get to the market right away.

Brand name pharmaceutical companies find various legal ways to extend their patent or market exclusivity to block generic competition. So as we review PDUFA, it would be beneficial to consider these related issues and look for ways in which we might adjust PDUFA to address them.

I understand that we expect two studies from the Administration on safety and effectiveness of PDUFA to be released later this year, and I think it would be a disservice to act on PDUFA for reauthorization without the benefit of those studies.

So I hope, Mr. Chairman, that you will not schedule a mark up until we have them in-hand, and to this end, I look forward to hearing our witnesses' testimony on this subject, and I look forward to working on this with you, Mr. Chairman, and I yield back my time.

[The prepared statement of Hon. Lois Capps follows:]

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

Mr. Chairman I appreciate the opportunity you are giving the subcommittee to review the Prescription Drug User Fee Act.

Prescription drugs have radically changed health care and improved the lives of millions of Americans. They have become an essential component of what is now standard medical care, at least for those who can afford it.

This committee has often struggled with issues relating to prescription drugs.

But whether we are talking about seniors on Medicare or pharmaceuticals for children there are basically three questions we ask as we discuss prescription drugs: How fast can a patient get them, how safe and effective are they, and how much do they cost.

We want them to be quick to market, safe to use, and affordable to patients.

PDUFA has addressed the first matter by significantly improving the FDA's ability to review and approve new medications.

These medications' quicker access to market seems to have helped many Americans enjoy a higher quality of life.

That being said PDUFA raises some questions about the issue of safety, and may contribute to some of our problems addressing cost.

In theory, while PDUFA accelerates the approval process for new drugs, these drugs still must be safe before they are approved.

But there is some concern that the performance goals of PDUFA end up putting drugs on the market before they are sufficiently tested and reviewed.

Post market surveillance is supposed to catch anything like this, but the resources for these surveys and FDA's authority to insist on them are limited.

This is certainly something we need to correct as we move towards reauthorization of PDUFA.

I am also worried that PDUFA may help keep the costs of prescription drugs inflated.

The fees themselves of course add cost to medications, but more importantly PDUFA also forces FDA resources towards the approval of brand name drugs, denying those resources for the review of generic drugs.

Generics access to the market is proven to lower the cost of prescription drugs dramatically, but the effect is limited because FDA is so slow to approve them.

In 2001, the average time it took to review and approve a new brand name drug was 12 months. FDA took nearly twice that long, 22 months on average, to approve generic drugs. This is appalling.

And even when these generics are approved, it does not necessarily mean that they get to market right away.

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As we review PDUFA, it would be beneficial to consider these related issues and look for ways we might adjust PDUFA to address them.

I understand that we expect two studies from the administration on the safety and effectiveness of PDUFA to be released later this year.

I think it would be a disservice for this subcommittee to act on PDUFA reauthorization without the benefit of those studies, and I hope, Mr. Chairman, that you will not schedule a markup until we have them in hand.

To this end I look forward to hearing our witnesses' testimony on this subject and I look forward to working on this with you Mr. Chairman.

Mr. BILIRAKIS. Mr. Buyer for an opening statement.

Mr. BUYER. I have just a couple of thoughts, Mr. Chairman. I think it is very valuable to America's society that our drug companies lead the world in the cutting edge in science and biologics.

I don't think we want to do anything that would dull that innovation and creativity of the greatest minds of the world. And there are so many countries out there that their governments have imposed systems that have had a detrimental impact upon those industries.

And they look to the United States and the great minds of the world come here. And we have to be very careful in what we do. So, sure, there are the pressures that different members receive from their constituencies to gain access to these great drugs because of what it can do for the quality of life or their loved one who is sick or ailing.

But Congress, and the industry, and the agency, did something right. You know, someone who is critical toward government, you also have to compliment when something was done right.

In 1992, something was done right. I think it is thoughtful for us to sort of look back now over the last 10 years and say, okay, what are some of the lessons learned. I believe that our process here in reauthorization should be the maintenance of something that works.

And not trying to change something, and not bring political agendas in an election year into something that is very critical and is something that we have to do, and that is reauthorize a successful program.

I will accept recommendations from the agency, and the industry will have some, and I think that is part of the oversight function of Congress to do. But we have to be very careful here not to miss something that is so successful. With that, I yield back.

Mr. BILIRAKIS. I thank the gentleman.

Mr. Strickland for an opening statement.

Mr. STRICKLAND. I want to thank you, Mr. Chairman, and Ranking member Brown, for this hearing today. I was pleased to read in the submitted testimony of the success since 1992 in speeding FDA's review times for drug applications.

The numbers are impressive. Median review times for priority drugs have decreased from a median of 20.5 months to 6 months, and the median review time for standard new drug applications fell from 26.9 months to about 12 months. PDUFA has meant that

more Americans have access to new remedies faster, and I am glad that we will reauthorize the program to continue these successes. However, I hope that we use the opportunity this reauthorization gives us to strengthen PDUFA and ensure that the program has not sacrificed safety for speed.

Since drugs are getting to the market and American consumers more quickly, we should consider the effects of this faster time line on drug safety and dedicate a portion of PDUFA's resources for FDA to track post-market outcomes of drugs.

Similarly, I believe we should take this opportunity to consider the effect of direct to consumer advertising on prescription drug use and cost. If PDUFA's triggers cause the FDA to devote less resources to functions like post-market tracking, and the review of direct to consumer ads, we should we think the way these triggers operate for the limits on the use of PDUFA funds.

This debate would not be complete without a consideration of the effects of faster review times on the cost of prescription drugs. I hear every day from Medicare beneficiaries, in particular, who are struggling to afford the cost of their prescription drugs.

Put in this context, even the shortest possible FDA review will not help those Americans who lack drug coverage to access the drugs. They need to live healthy and productive lives.

And that is an issue that this Congress must address and should address this year. I want to thank you, Mr. Chairman, and I yield back the remainder of my time.

Mr. BILIRAKIS. I thank the gentleman. I ask for unanimous consent, first of all, that the opening statements of all members of the subcommittee be made a part of the record, and without objection, that will be the case.

[Additional statements submitted for the record follow:]

PREPARED STATEMENT OF HON. FRED UPTON, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Mr. Chairman, thank you for holding today's hearing on the reauthorization of the Prescription Drug User Fee Act. I am sure that we will hear a lot of statistics this morning about the impact that this important law has had on improving both the quality and the timeliness of the review and approval of new drugs and biologics. But I want to focus on the difference that this law has made in the lives of individuals—of friends and family members who have greatly benefited by the FDA's ability to give timely review and approval to potentially life-saving drugs and biologics.

Just about a year ago, a call came into my district office from a constituent asking if we could do anything to speed the FDA's review of a very promising new drug—Gleevec—for the treatment of the rare form of leukemia with which her husband was suffering. Like very many in the Kalamazoo community, my staff and I have known and valued the friendship of this couple for many years. As was typical, her husband "didn't want to bother us" with their problems, our constituent reported, but she was very worried. We knew he had been suffering from leukemia, but until that call, we didn't know that the medication he was taking was no longer effective in controlling it and that his condition was deteriorating. This drug may well have been his last hope.

We checked with the manufacturer and learned that the FDA appeared to be very close to approving the drug. That proved to be the case. Within a week or so of the call, the FDA approved Gleevec, and we worked with Novartis to get the drug to our constituent's hospital pharmacy. It has proved to be the miracle we were all praying for. He is back on his feet enjoying life, and my life and the lives of so many in our community who know them and treasure their kindness and friendship are the richer for his recovery, too.

In all likelihood, this would not have happened before we enacted user fees and the FDA Modernization Act, which together give the FDA the flexibility and resources it needs to review and approve Gleevec and similar, breakthrough drugs.

Recognizing the promise of this drug, the FDA reviewed the marketing application in less than three months under its accelerated approval regulations. That is a record—the fastest ever approval for an oncology drug.

I know we will hear today from those who are concerned that perhaps the agency is moving too fast on new drug approvals. But had the agency not acted with the speed and expertise it did on Gleevec, my friend and constituent would probably not be with us today. There is a human cost—a great cost—in delaying this reauthorization.

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

The Prescription Drug User Fee Act (PDUFA) is, in large part, what separates the United States from the rest of the world when it comes to consumer access to innovator drugs.

No one rivals this country in the manufacturing, approval, and distribution of innovator pharmaceutical products and devices—thanks to PDUFA. I would like to see that continue.

The issue we face at this point is how do we do it even better?, especially since funds needed for the drug approval process at FDA outweigh the revenue coming in through drug application fees.

The last thing any of us wants is to see drug safety and approval time slip because FDA does not have what it needs to get the job done.

PDUFA must be reauthorized this year, not only for the sake of patients everywhere but for the continued high standard of innovation set by this country.

My interest today is to better understand the recent agreement reached between the FDA and industry on application fees and performance standards.

Since this agreement is paramount in any PDUFA reauthorization we attempt, it is important we give our full attention to our witnesses today.

With that, Mr. Chairman, I yield back my time.

PREPARED STATEMENT OF HON. ROBERT L. EHRLICH, JR., A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MARYLAND

Mr. Chairman, thank you for holding this important hearing to discuss the reauthorization of the Prescription Drug User Fee Act (PDUFA).

PDUFA, which was first enacted in 1992, authorizes FDA to charge pharmaceutical companies user fees to expedite the review process for human drug and biologic applications. There are three types of fees: 1) application fees are paid when human drug applications or supplements are submitted; 2) product fees are due annually for each marketed prescription drug product; and 3) establishment fees are also due annually for each establishment manufacturing prescription drugs.

Mr. Chairman, reauthorization of this legislation is critical. The federal government must have in place at the FDA an effective procedure with sufficient resources, personnel, and expertise to review new drugs to ensure that the American population receives speedy access to the cutting-edge drugs available to treat so many health conditions today. PDUFA has worked to significantly reduce approval times.

For their part, the biotechnology and pharmaceutical companies should have the guarantee of an expedited, streamlined administrative review process to ensure that their innovations are reviewed thoroughly and sent to market as soon as possible for safe consumption. To ensure speedy review, companies must pay the costs of the application, product, and manufacturing fees so FDA has the resources to do its job right.

Mr. Chairman, as Co-Chair of the Congressional Biotechnology Caucus, and recognizing the over 270 biotechnology companies in Maryland, I know that it is critical that new drug treatments receive expeditious, thorough scrutiny of their latest products.

Ultimately, this legislation is about patients, and as we work with all groups to ensure an effective review process, we must keep patient safety and speedy access to medical innovations in mind.

I look forward to the testimony today as we consider reauthorizing this important legislation.

Thank you, Mr. Chairman.

PREPARED STATEMENT OF HON. ED TOWNS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW YORK

Today's hearing gives us another opportunity to promote a unique relationship between government and industry: the reauthorization of the Prescription Drug User Fee Act (PDUFA). PDUFA is a successful partnership that allow the F.D.A. to collect user fees from the pharmaceutical industry in order to hire additional drug reviewers and accelerate the drug review process.

By all accounts, the program has been extremely successful in bringing new drugs to market in a more reasonable timeframe. For example, before this legislation was enacted by this committee in 1992, review times for new drug entities averaged about 2.5 years. By 1999, the average review time had been reduced to 12.6 months. I am aware that some have criticized this legislation as compromising F.D.A.'s independent review authority. It is important to ensure that the enhanced efficiency of the drug review process has not compromised drug safety. Therefore, I am anxious and eager to learn whether drug withdrawals can, in fact, be traced to faster approval times.

Finally, Mr. Chairman, we should remember that the reauthorization of PDUFA will not only determine whether 1,000 drug reviewers will keep their jobs past July of this year but it could also well determine how quickly we approve a new treatment for diabetes, lupus or cystic fibrosis or many other diseases. Certainly, we should examine proposals to strengthen "post-market surveillance." The F.D.A. has designed a new proposal which allows the drug sponsor to design the appropriate studies to monitor and assess potential risks. This approach process allow quality to be built in from the beginning of the review process. We should also remember that this law, in its current form, has been remarkably effective in bringing additional resources to the F.D.A. as well as reducing the market approval time for drugs. I am hopeful that this committee can continue to provide the kind of policy leadership which has resulted in new, faster drug approvals with the safety and efficacy standards which has previously characterized F.D.A. reviews. I look forward to hearing from today's witnesses.

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

Thank you Mr. Chairman for holding this hearing today on the Prescription Drug User Fee Act.

When the PDUFA program was first authorized in 1992, there were many critics who worried that it would be a conflict of interests for the FDA to accept user fees in order to expedite the review of pharmaceuticals and biologics.

And while there are still critics of the PDUFA program, the evidence indicates that the FDA and the industry can work together in a fashion that gets life-saving medicines to the public in an efficient and safe manner.

In 1993, the median review time for a standard new drug application was almost 26 months.

For an individual dying of a serious illness, this was far too long of a wait.

Since PDUFA's implementation, however, there has been a dramatic decrease in the length of time it takes to have a new drug approved. Today, the median has dropped to just twelve months.

More importantly, for priority new drug applications—which are the life-saving therapies that often represent the last hope for people with serious terminal illnesses—the median approval time was six months in 2001.

As Dr. Crawford points out, the life-saving breast cancer treatment, Herceptin, was approved by FDA in less than five months.

This is exactly the kind of result that the Congress intended when it passed this law a decade ago.

PDUFA is not without its problems, however, and that is what we are here today to discuss.

A common complaint from both consumer groups and FDA alike, is that "sweat shop" conditions have impacted employees at FDA, prohibiting them from attending continuing education classes, raising their stress levels, and resulting in high turnover.

This environment is not only bad for employees, but it's bad for the process.

Training scientists takes a tremendous amount of time and resources. The loss of those human resources impacts the ability of the FDA to do its job.

There is also a real shortage of financial resources at FDA.

Many have expressed concern that PDUFA is crowding out other non-PDUFA programs, such as post market surveillance, approval for generic pharmaceuticals, and oversight of direct-to-consumer marketing.

It is important that the activities at FDA be balanced and that adequate resources are provided to ensure that FDA can meet its mission.

Mr. Chairman, these are important issues and I am glad that we are holding a hearing to learn more about them.

It is certainly of importance to all of my constituents that the FDA has the resources it needs to review pharmaceuticals to ensure their safety and efficacy.

But I would be remiss if I did not raise other concerns about prescription drugs—the costs of these vital medications, the affects of direct-to-consumer advertising, and the absence of a Medicare prescription drug benefit.

Last year, the National Institute for Health Care Management Foundation stated that spending on retail outpatient prescription drugs rose by almost 19% in 2000, from $111.1 billion to $131.9 billion.

Approximately half of that spending increase can be attributed to just 23 drugs.

Among those drugs are blockbuster drugs like Vioxx, Lipitor, Celebrex, and Glucophage the very drugs that seniors rely on every day to treat chronic, long-term illnesses like diabetes, arthritis, and high cholesterol.

It is no coincidence that these are the same drugs that are so heavily advertised in direct-to-consumer marketing.

We must ensure that patients understand what these drugs do—and don't do—and the risks associated with taking them.

But most importantly, after decades of rhetoric, the Congress must act to provide a meaningful, comprehensive prescription drug benefit under Medicare.

A full one-third of Medicare beneficiaries—more than 14 million seniors—have no prescription drug coverage at all.

We need a prescription drug benefit that makes sure that seniors, who have worked hard and paid taxes their whole lives, have access to these life-saving medications.

The Congress has been slow to act on this issue, and it is inexcusable.

But I have to give credit where credit is due. Recently, various companies in the pharmaceutical industry have announced discount cards and programs for low-income seniors who do not have access to a prescription drug benefit.

Just yesterday, Eli Lilly joined the ranks of Pfizer, Novartis and GlaxoSmithKline and announced the creation of their prescription drug discount program.

These programs are by no means a solution to the Medicare prescription drug problem but these companies have made an effort to help the poorest seniors get access to the drugs they need.

I thank them for their efforts in this regard, and hope that they will prompt Congress to do the same.

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

Mr. BILIRAKIS. I also ask for the unanimous consent that a couple of documents here, one entitled, "Patient and Consumer Coalition, Background of Prescription Drug User Fee Act," and also a letter to the four chairmen and ranking members from a group of organizations, and it doesn't have a date on it, but these have been shared with the minority, that they be made a part of the record. That being the case, and without objection, they are so made a part of the record.

[The information referred to follows:]

The Honorable W.J. BILLY TAUZIN
Chairman
Energy and Commerce Committee

The Honorable JOHN DINGELL
Ranking Member
Energy and Commerce Committee

The Honorable MIKE BILIRAKIS
Chairmnan
Health Subcommittee

The Honorable SHERROD BROWN
Ranking Member
Health Subcommittee

DEAR CHAIRMEN AND RANKING MEMBERS: We, the undersigned patient advocacy organizations implore you to consider a swift and clean reauthorization of the Prescription Drug User Fee Act (PDUFA) that has been of enormous benefit to patients with all types of diseases in all parts of our country.

The user-fee law has been an unqualified success—a poster child for Congressional achievement. Before the law was first enacted ten years ago, review of new drugs took about 2½ years and the timeliness of drug review was a big concern to patients who were not so patiently waiting for their life-saving medicine.

Countless thousands of patients have benefited from Congress' leadership in enacting the first PDUFA law in 1992, and supporting its reauthorization in 1997. Since that time, life-saving drugs have been made available to patients sooner, and without in any way compromising the gold standard of drug approval upon which patients rely. According to the FDA, the rate of drug withdrawal has remained constant at 2.7 percent before 1992 and 2.7 percent today.

The result: the average review time for new drugs has been cut almost in half from 30 months to less than 18 months—for some patients, that's a lifetime. And today, about half of all new drugs are approved first in the U.S.

The law is working. Patients are not waiting as long for their new medicines—and Congress must act without delay to ensure that patients continue to receive new cures and treatments as expeditiously as possible. Moreover, it is vital that PDUFA, which is set to sunset on September 30, be reauthorized by July so FDA does not have to begin laying off reviewers and the drug approval process is not disrupted in other ways.

Our organizations represent literally millions of American patients and their families. We are all depending on your leadership to reauthorize PDUFA cleanly and quickly.

THE ALS ASSOCIATION; LEUKEMIA AND LYMPHOMA SOCIETY;
PARKINSONS DISEASE FOUNDATION; AMERICAN ASSOCIATION OF
CLINICAL ENDOCRINOLOGISTS; PANCREATIC CANCER ACTION NETWORK;
KIDNEY CANCER ASSOCIATION; CANCER RESEARCH INSTITUTE;
ASSOCIATION OF CLINICIANS FOR THE UNDERSERVED; NATIONAL ALLIANCE
FOR HISPANIC HEALTH; NATIONAL AIDS TREATMENT ADVOCACY PROJECT;
CANCER RESEARCH FOUNDATION OF AMERICA; AMERICAN LIVER FOUNDATION;
PULMONARY HYPERTENSION ASSOCIATION; AMERICAN FOUNDATION
FOR UROLOGIC DISEASE; CYSTIC FIBROSIS FOUNDATION;
AND NATIONAL COALITION FOR WOMEN WITH HEART DISEASE

PATIENT AND CONSUMER COALITION

BACKGROUND ON THE PRESCRIPTION DRUG USER FEE ACT

The Prescription Drug User Fee Act was enacted in 1992 to address concerns about the length of time it took for new drugs treating life-threatening and disabling conditions—especially AIDS—to be reviewed and approved by the FDA. The authors of PDUFA recognize that Congress was not going to provide enough in new appropriations to support the increased staff that a shorter approval process would require. PDUFA mandated that drug manufacturers pay user fees when they filed a New Drug Application for review and approval of a product.

PDUFA was reauthorized in 1997 as part of the Food and Drug Administration Modernization Act. However, this iteration included more stringent "performance goals" requiring that the FDA meet very tight review deadlines. These faster deadlines were insisted upon by the pharmaceutical industry, which argued that these "measurables" were necessary to ensure that the user fees they paid were not dis-

persed to fund other agency activities. For the first time, PDUFA II also included stipulated time frames for the scheduling of meetings and response to industry requests ("management goals").

As a result of PDUFA I and II, the FDA has both dramatically increased the amount of resources it devotes to new drug and biologics review and decreased the review time. But this has come at a price. PDUFA requires that the agency increase funding from non-user fee revenues for drug reviews by an inflation-adjusted amount every year. But, Congressional appropriations for the FDA have not kept pace with inflation and with the increased mandates on and responsibilities of the agency. As a result, the only way the FDA can comply with PDUFA's requirements to increase non-user fee funding for the drug review process is to take resources away from other essential activities, such as post-market research and surveillance, on-site inspections, and regulation of medical devices. Moreover, the agency has said that user fees generate less than the total expenditures the agency must make to satisfy PDUFA performance and management goals. As Former Commissioner Jane Henney said, "...the truth is, the program is barely surviving because of the way it was designed. We don't have the resources to do the things we believe are essential, such as adverse event reporting, because they are not supported by PDUFA funds."[1]

The short review times mandated under PDUFA II have had other negative effects. The director of FDA's Center for Drug Evaluation and Research, Dr. Janet Woodcock, has expressed a great deal of concern about the high rate of turnover among review staff, which means that the agency has had difficulty retaining experienced, competent reviewers. Dr. Woodcock has said that the intense timelines under PDUFA have created a "sweatshop environment that's causing high staffing turnover."[2]

There have also been concerns about a series of high-profile drug withdrawals over the last few years. According to the Pulitzer Prize-winning investigation by David Willman of the *Los Angeles Times,* seven of these drugs—Lotronex, Propulsid, Rezulin, Raxar, Posicor, Duract and Redux—are suspected in 1,002 deaths.[3] While FDA officials claim that these safety problems were not necessarily linked to PDUFA, the withdrawals raise troubling questions about whether the agency performance goals mandated by the Act may be overriding its public health responsibilities.

In fact, several former FDA employees told the *Los Angeles Times* that they were under a great deal of pressure to approve drugs quickly. Bill Schultz, former deputy commissioner at the FDA said, "You can meet the [performance] goal by either approving the drug or denying the approval. But there are some who argue that what Congress really wanted was not just decisions, but approvals. That is what gets dangerous." Dr. Solomon Sobel, the former director of the FDA's metabolic and endocrine drugs division told the *Los Angeles Times* that deadline pressure under PDUFA was not just to make decisions: "The pressure to meet deadlines is enormous. The basic message is to approve."[4]

REAUTHORIZATION OF THE PRESCRIPTION DRUG USER FEE ACT

The undersigned members of the Patient and Consumer Coalition believe that the upcoming re-authorization of PDUFA offers an important opportunity to increase the safety of prescription drugs and devices in this country and to insure that the protection of the public's health is the FDA's top priority under the Act. We urge Congress to:

- *Hold balanced hearings on PDUFA reauthorization and drug safety concerns.* The hearings should include testimony from patients who have been harmed by problem drugs—or their representatives—and consumer advocates who are knowledgeable about PDUFA. Such hearings would send a vital signal to FDA from Congress that what the public wants and deserves is a thorough review and oversight process for drugs and biologics, not just speedy approval of new products.
- *Adequately fund the entire range of FDA's approval and safety oversight activities from general revenues.* There is an urgent need for increased funding for post-marketing surveillance and other safety-related activities not covered by current

[1] FDA Consumer Magazine, "User Fees for Faster Drug Review: Are They Helping or Hurting the Public Health?," September-October 2000.
[2] Ibid.
[3] David Willman, "How a New Policy Led to Seven Deadly Drugs," *Los Angeles Times,* December 20, 2000.
[4] Ibid.

user fees. User fees are not a substitute for adequate federal funding of these vital and growing public health functions. Adherence to this principle would be the surest way to remove the worrisome potential for conflict-of-interest that arises when dedicated income streams flow to the regulator from the regulated industry.

- *Give the FDA total control over all review and surveillance activities.* If an unwillingness to appropriate adequate funds leads Congress to consider the expansion of user fees, it is absolutely essential that the FDA alone determine their usage, without the kind of inappropriate control over the use of these fees (through mandated decision-making deadlines) that the industry has exercised with new drug approvals.
- *Address drug safety concerns created by PDUFA's excessive and inappropriate focus on swift approval over public health.* PDUFA III should include new safety protections that, to the greatest extent possible, protect the public from potential harm caused by adverse reactions, side effects and adverse events related to pharmaceutical products and biologics. Decision-making deadlines for drug review should be redefined to focus on the FDA's responsibility to guarantee safe drugs, not only on the speed with which reviews are conducted. The agency's antiquated and under-funded adverse event reporting system (for drugs, biologics and devices) should also be modernized.

1. Restructure User Fees

- *Eliminate the linkage between appropriated and user fee funds.* The current law results in disproportionate funding for the drug approval process compared to most other research, regulatory, and public education functions. At a minimum, the program must be re-designed in such a way as to prevent the draining of funds from vital FDA functions.
- *Require that user fees support the life cycle of the review process.* Presently, FDA staff hold numerous pre-New Drug Application meetings with manufacturers before the agency receives any PDUFA fees for the intended application. While these meetings benefit sponsors greatly by improving their understanding of FDA expectations and the quality of their applications, they also divert FDA staff time from other review functions and increase the cost and difficulty of meeting PDUFA goals. In other words, the required meetings are an un-funded mandate on the agency.

2. Eliminate or Overhaul Performance Goals

Although PDUFA's deadlines are for decision-making on drugs and biologics, not approval, these goals put the FDA under tremendous financial pressure to move very quickly on the overall approval process. By requiring that decisions must be made within the same timeframes for priority and standard reviews,[5] these goals force the agency to take an unvarying, "cookie cutter" approach to approvals. Congress should eliminate these required goals. If this does not occur, the agency should be given greater flexibility to set its own priorities and/or extend the goals, including:

- *Consult All Stakeholders*—If performance goals are not eliminated in PDUFA III, consumers and patient representatives should be involved in developing them.
- *Grant FDA a "Scientific Override"*—When the FDA requires additional information or clarification from the manufacturer as part of the review process, the FDA should be allowed to "stop the clock" on review deadlines while waiting for this information to be provided.
- *Eliminate Rigid Management Goals*—These goals require the agency to set up meetings with the industry within specific timeframes. They should be replaced by a more flexible system that allows the FDA to prioritize these requests, thus decreasing undue burden on the agency.
- *Allow FDA More Flexibility For Standard Reviews*—There is no public health justification for requiring the FDA to decide on a "me too" drug that duplicates therapies already on the market at the same speed as a drug that might offer therapeutic advantages to some patients. The FDA should be granted greater authority to prioritize the review of standard drug applications.
- *Create Safety Goals*—FDA should establish performance goals oriented toward protecting the health and welfare of consumers, such as tracking and reviewing Phase IV trials, improving the collection, analysis and response of adverse event

[5] PDUFA II establishes deadlines that require FDA to review 90 percent of priority ("fast track") new drug Applications within 180 days and 90 of standard applications within ten months.

reports, and enhancing the speed and quality of review of direct-to-consumer advertisements.

3. Enhance Drug Safety Measures and FDA Enforcement Authority

- *Grant FDA Civil Monetary Fine Authority and Subpoena Power*—When companies fail to complete Phase IV confirmatory trials or when companies repeatedly violate prescriber and direct-to-consumer advertising guidelines, the agency should be given the authority to levy significant monetary penalties.[6] The agency should also have the power to compel companies to produce relevant documents.[7]
- *Launch Independent Drug Withdrawal Investigations*—An office or agency independent of the FDA should investigate the circumstances surrounding the withdrawal of medical products from the market, as the National Transportation Safety Board does for plane crashes.
- *Increase Monitoring and Review of Phase IV Trials*—Require the FDA to track Phase IV trials, strictly monitor and enforce the informed consent and protection of human subjects in those studies, and, in a timely manner, review the quality of the studies and the accuracy of the findings.
- *Improve Adverse Event Reporting*—Hospitals, HMOs, nursing homes and other healthcare providers should be required to automatically report (the present system is voluntary) serious adverse drug events, adverse reactions and medical errors to the FDA, CDC, and/or other relevant agencies. Appropriations for FDA's oversight of adverse event reporting should be dramatically increased.
- *Utilize the Centers for Education and Research on Therapeutics*—CERTS should examine the feasibility of: (1) implementing a patient self-monitoring reporting system for signaling possible adverse drug reactions;[8] and, (2) expanding the use of medical registries to follow patients who may be at risk of serious reactions
- *Broaden Distribution of medication Guides*—Consumers should be given power to make informed decisions about drugs and devices and to avoid preventable harm. It is time to mandate that medication guides with scientifically accurate, unbiased and clearly worded information about the risks and benefits of a treatment be included with every dispensed drug (as proposed by the FDA in 1995.) Such medication guides would also, for the first time, provide a mechanism for notifying consumers directly when new safety concerns about a drug emerge that require a change in a drug's approved labeling.
- *Provide Consumers with More Post-Market Drug Safety Information*—Section 506B of the Food, Drug and Cosmetics Act should be amended to expand the scope of information made available to the public to include information as study protocols, patient accrual rates, reports of unexpected, i.e., unlabeled, suspected adverse reactions, and study results.[9]
- *Scrutinize Single Controlled Clinical Studies*—An increasing number of drug manufacturers have indicated that they will begin submitting new drug applications

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[6] As a condition of approval of a new drug by the agency, drug companies often commit to doing post-marketing or Phase IV studies. These studies can help to identify previously unknown dangers presented by a new drug so that its safety labeling can be updated or if necessary the drug can be withdrawn. According to a *Public Citizen* report released in 2000, of the 88 new drugs that were approved between 1990 and 1994 with the understanding that the sponsor would complete at least one post-marketing study, only 13 percent (11 of 88) had completed all of the studies they had agreed to as of December 1999.

[7] According to a 1990 Congressional Research Service study, almost every other U.S. health and safety regulatory agency has subpoena power. Without the ability to subpoena company records, the FDA's efforts to assure drug safety are hamstrung. The case of the FDA's post-approval investigation of the drug Halcion demonstrates the problems the agency faces. In that case, the agency could not subpoena the company's records even though it had suspicions of criminal wrongdoing. At one point in that investigation, the agency even went so far as to ask for the intervention of a federal judge to modify a gag order in a tort action against the maker of Halcion so that the agency could have access to crucial documents.

[8] Under this system, suggested by Seymour Fisher and Stephen G. Bryant, patients would be given information about how to report adverse drug reactions by their pharmacist. This system would make it possible to compare the rates of adverse drug reactions to a new drug with drugs already on the market for the same indication. (S. Fisher, S.G. Bryant, "Postmarketing surveillance of adverse drug reactions: patient self-monitoring" Journal of the American Board of Family Practice, 1992; 5:17-25.)

[9] Under its proposed rule of December 1999 implementing FDAMA's requirement for the industry to report its progress on completion of phase IV tests to the agency this information would have been made available to the public. However the industry objected, claiming that FDAMA did not give the agency the authority to make this information public and this requirement was removed from the final rule, which was published in October of 2000. Legislation is needed to clearly give the agency the authority it needs to disclose this information.

using data from only one controlled clinical study, which is now allowed by law, rather than multiple studies. An independent study should be conducted at an appropriate time to assess the effectiveness of single controlled studies in assessing the safety of drugs and biologics.

- *Examine Comparative Safety Data*—Manufacturers should be required, as part of their application to the FDA to market a new drug or biologic, to submit the results of tests comparing the safety and efficacy of their product to others already on the market that are used to treat the same indication.

This position paper is endorsed by the following members of the Patient and Consumer Coalition: the Alpha I Foundation; Center for Medical Consumers; Consumer Federation of America; Gray Panthers; International Union, UAW; the National Consumers League; the National Organization for Rare Disorders; the National Center for Policy Research for Women & Families; the National Women's Health Network; and the Title II Community AIDS National Network.

Mr. BILIRAKIS. And having waited very patiently, is Dr. Lester M. Crawford, Deputy Commissioner of the Food and Drug Administration. Dr. Crawford, thank you very much for being here, and proceed, sir.

We are going to set the clock at 10 minutes, and you do what you can, and we won't worry about the clock.

STATEMENT OF HON. LESTER M. CRAWFORD, DEPUTY COMMISSIONER, FOOD AND DRUG ADMINISTRATION; ACCOMPANIED BY JANET WOODCOCK, DIRECTOR, CENTER FOR DRUG EVALUATION AND RESEARCH; AND CATHERINE ZOON, DIRECTOR, BIOLOGICS EVALUATION AND RESEARCH

Mr. CRAWFORD. Thank you very much, Mr. Chairman, we thank you and the other members for scheduling today's hearing. I am joined at the table by Dr. Janet Woodcock, who is the Director for the Center for Drug Evaluation and Research; and Dr. Catherine Zoon, who is the Director of the Center for Biologics Evaluation and Research.

I have a written statement for the record, and I will confine my remarks to within the 10 minutes. In my oral remarks, I will describe the Agency's success in implementing the Prescription Drug User Fee Act, identify priorities for PDUFA-3, and emphasize the importance of reauthorizing this law in advance of its September 30, 2002 expiration date.

PDUFA has been a remarkable success. Since PDUFA was enacted in 1992, the FDA has met the highest expectations for performance, while continuing to adhere to rigorous standards for safety and effectiveness.

We now have 8 years of data on our efforts to achieve PDUFA goals. During this period the FDA faced a total of 73 performance goals. We met or exceeded 71 of those goals.

If you add procedural goals to that total, the Agency met or exceeded 86 out of 92 PDUFA goals. The result has been a dramatic reduction in product approval times. Drugs are now reviewed in the U.S. as fast or faster than anywhere in the world, without compromising the very stringent standards that Americans have come to expect.

With the enactment of PDUFA, U.S. companies have overtaken their European counterparts, and now have a commanding lead in world markets. A July 2001 report found that the European share of the world pharmaceutical market fell by 10 percent over the past decade, while the U.S. market share rose by more than 10 percent.

During the same period U.S. research and development increased a remarkable five-fold, and that is why the Tufts University Center for the Study of Drug Development declared that the U.S. environment for pharmaceutical innovation since PDUFA is nothing short of remarkable.

The membership of this Subcommittee deserves a large share of the credit for championing PDUFA and for making this record of achievement possible. Your efforts have produced significant benefits for public health.

The public has gained access to 717 new drugs and biologics under PDUFA. These include important new products to treat cancer, AIDS, cardiovascular disease, and to fight infection.

Every day the lives of patients are immeasurably improved as a result of the great emphasis on priority review that we instituted under PDUFA. While our experience under PDUFA-2 has generally been good, significant issues have surfaced that undermine the program's financial foundation.

During the final 3 years of PDUFA-2, fee revenue has been less than the cost of performing review activities. The FDA has been able to sustain its review effort by spending fee revenue collected in previous years that has been held in reserve.

However, unspent revenues from previous years will be depleted by September 30. A top priority will be to establish a fee structure to ensure that income covers the cost of PDUFA enhancements to the drug and biologic review process.

Funding a program of risk assessment for PDUFA drugs and biologics is a second priority. While drugs and biological products are under development, clinical testing is usually limited to small, carefully selected populations.

After approval, when the drug reaches a much larger and diverse population, adverse events not seen during clinical trials may emerge. I want to emphasize that there is no evidence that drugs are being withdrawn from the market for safety reasons at a greater rate during the PDUFA era.

In fact, the withdrawal rate for new drugs approved prior to PDUFA is identical to the withdrawal rate for drugs approved since PDUFA was enacted. However, a more effective program of risk management for new drugs that improve patient safety is warranted by the reality that more drugs are launched for the first time in the U.S.

Mr. Chairman, PDUFA-2 expires on September 30, 2002. I want to emphasize again the importance of achieving a timely reauthorization of this law. If we are to sustain our record of accomplishment under PDUFA-2, it is critical that reauthorization occur without a gap between the expiration of the old law and the enactment of PDUFA-3.

Retaining FDA's skilled employees is essential to the success of PDUFA-3. A delay in the reauthorization of this program may precipitate an 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, and rebuilding the infrastructure that we would lose in such an event would be very difficult indeed. Thank you for your com-

mitment to the mission of the FDA, and to the continued success of PDUFA.

Thank you very much.

[The prepared statement of Hon. Lester M. Crawford follows:]

PREPARED STATEMENT OF HON. LESTER M. CRAWFORD, DEPUTY COMMISSIONER, FOOD AND DRUG ADMINISTRATION

INTRODUCTION

Mr. Chairman and Members of the Subcommittee, I am Lester M. Crawford, Deputy Commissioner of the Food and Drug Administration (FDA or the Agency). I am pleased to be here today to discuss the Agency's success in implementing the Prescription Drug User Fee Act and to emphasize the importance of reauthorizing this law in advance of its September 30, 2002, expiration date.

BACKGROUND

In 1992, Congress enacted the Prescription Drug User Fee Act (PDUFA I). This law provided additional resources to hire more medical and scientific reviewers to conduct premarket reviews, to hire support personnel and field investigators to speed up the application review process for human drug and biological products, and to acquire and support critical information technology infrastructure.

In 1997, after the success of PDUFA I, Congress reauthorized the program for an additional five years. With this reauthorization (PDUFA II), came higher expectations for reviews and additional goals designed to reduce clinical drug development times. The President's budget request for Fiscal Year (FY) 2003 recommends that PDUFA be reauthorized through FY2007, and we have been engaged in discussions with consumers, health providers, and industry over the past year to develop proposals for PDUFA III. These discussions have been very useful, and we hope to complete the consultation process in the very near future and forward our PDUFA III recommendations to the Department of Health and Human Services.

PDUFA ACHIEVEMENTS

During PDUFA I and PDUFA II, FDA met the highest expectations for performance while continuing to adhere to rigorous standards for safety and effectiveness. We now have eight years of data on our efforts to achieve PDUFA goals, and the Agency's record of achievement is impressive. The Agency faced a total of 73 performance goals during this period. These goals governed the review of priority and standard new product applications, resubmitted applications, and supplements. During this eight-year timeframe, FDA met or exceeded 71 of 73 PDUFA performance goals.

In addition to the 73 performance goals, procedural and processing standards were instituted under PDUFA II. A total of 19 goals governing meetings, clinical holds, dispute resolution, and special protocols were established when the law was reauthorized. FDA met or exceeded 15 of 19 procedural and processing goals. If you combine our performance and procedural accomplishments, the Agency met or exceeded 86 out of 92 PDUFA goals.

Not only has FDA significantly reduced application review times under PDUFA, it also has significantly reduced product approval times, and therefore, the time for new drugs to reach the market. Review time is the time it takes FDA to review original or resubmitted new product applications, efficacy supplements, and manufacturing supplements and issue an action letter. Approval time is measured from the date an application was initially submitted to the date an approval letter is issued. Approval time includes the period of FDA review, as well as the time a sponsor may spend responding to deficiencies identified by the Agency during application review. Because of these deficiencies, some products require more than one review cycle. While PDUFA established goals for review times, and faster reviews tend to produce quicker approvals, the quality and completeness of an individual application and the public health priority of the product significantly affect time to approval.

The result of our efforts has been a dramatic reduction in product approval times. The median approval time for priority new drug and biologic applications dropped from 13 months in FY1993 to only six months in FY2000. We do not have complete data for FY2001, but median approval times are projected to remain at six months.

For standard new drug applications, the median approval time was 22 months in FY1993. By FY1999, however, median approval times had declined to 12 months. For a variety of reasons, such as competing PDUFA goals and priorities and unanswered questions that must be addressed within some applications, we may experi-

ence a slight increase in approval time in FY2000 for this category of applications. The data for FY2000 are only preliminary, however.

THE WORLD LEADER

Drugs are now reviewed in the U.S. as fast or faster than anywhere in the world, without compromising the very stringent standards that Americans have come to expect. Between FY1993 and FY 2001, pharmaceutical firms have introduced 285 new molecular entities (NMEs) and 73 biologics into the market, a dramatic increase compared to any other period of time.

Ten years ago, European pharmaceutical companies were the industry leaders. With the enactment of PDUFA, however, U.S. companies have overtaken their European counterparts and now have a commanding lead in world markets. According to a July 2001 report in the Financial Times, the European share of the world pharmaceutical market fell from 32 to 22 percent over the past ten years while U.S. market share rose from 31 to 43 percent. During this period, pharmaceutical R&D investment doubled in the European Union, while U.S. R&D increased a remarkable five-fold.

This turn-around prompted the Tufts Center for the Study of Drug Development to describe the U.S. environment for pharmaceutical innovation since PDUFA as "nothing short of remarkable.'" The members of this Subcommittee deserve a large share of the credit for championing PDUFA and for making these successes possible.

PDUFA RESULTS

Your efforts have produced significant benefits for public health. The public has gained access to 717 new drugs and biologics under PDUFA, including 174 that represent significant therapeutic advancements. During the PDUFA era, FDA reviewers have approved:

- 30 new medicines for cancer;
- 37 new medicines for AIDS;
- 29 medicines to fight infection; and
- 18 medicines for cardiovascular disease.

Every day, the lives of cancer patients are measurably improved as a result of the greater emphasis on priority review that we instituted under PDUFA. For example, Herceptin®, a biological product to treat breast cancer, was approved by FDA in less than five months. In Europe, the approval process took 18 months. Because of FDA's priority review, 10,000 American women with advanced breast cancer had earlier access to this drug. These patients will gain an estimated 2,300 additional years of life because of early access to this important new therapy.

The pharmaceutical industry also enjoys significant R&D savings as a result of shorter review times. Under PDUFA, FDA reduced new drug review by 12 months. Each month of reduced review results in an average saving of $2.5 million, or $30 million in R&D cost savings over 12 months. Given that FDA approves an average of 40 NMEs and biologics per year, the savings to industry represent $1.2 billion annually. The program represents a bargain in light of the $133 million that industry paid in user fees in FY2001.

Finally, PDUFA has also brought significant benefits for FDA:

- Performance goals have helped streamline and harmonize the management of drug and biological product review.
- The program's requirement for comprehensive product reviews and responses has resulted in improvements to the quality of the application review process.
- Most importantly, the fees have enabled the Agency to hire additional medical reviewers and other specialists, and upgrade the technology that is essential for the success of the program.

FDA GOALS FOR PDUFA III

1. Sound Financial Footing

While our experience under PDUFA II has generally been good, a number of significant issues have surfaced that undermine the program's financial foundation. In PDUFA III, we are working to address these issues and ensure that the Agency has a sound financial footing to conduct essential review and approval activities.

During the final three years of PDUFA II, the amount of fees collected has been substantially less than the cost of performing review activities. FDA has been able to sustain its review effort only by spending fee revenue collected in previous years that has been held in reserve—an arrangement permitted under the Act. In FY2001 and FY2002, spending from fee revenues will exceed fee income by about $30 million each year. FDA is reducing operations in FY2002 to adjust to this revenue shortfall.

However, unspent revenues from previous years will be depleted by the end of this fiscal year and there will be little or no fee balances available after September 30. Establishing a fee structure to ensure that income covers the cost of enhancements to the drug and biologic review process authorized by PDUFA is an issue that we are working to address in PDUFA III.

Another problem is that PDUFA application fees are only paid on new drug and biologic applications and efficacy supplements. Yet the review of fee-paying applications represents only a fraction of FDA's actual review workload. There are many activities associated with the process for the review of human drugs and biological products that are not covered by PDUFA fees. These activities continue to grow steadily and demand more resources each year, while the number of fee-paying applications, and the revenue they generate, fluctuates considerably. This dynamic was not taken into account when the fee formula was established.

The uncertainty about fee revenue is further complicated by the relationship between application fees and the product and establishment fees that also we collect under PDUFA II. The law directs that establishment and product fees rise and fall based upon the number of fee-paying applications, yet the volume of work associated with these activities has little or no relationship to the number of applications. The reality of this situation is inconsistent with the expectation that product and establishment fees were intended to be a stable element of PDUFA revenue in order to insure a consistent and predictable source of fees.2. Risk Management

While drugs and biological products are under development, clinical testing is usually limited to small, carefully selected populations of 5,000 or less. After approval, however, millions of patients may be exposed to the drug. When the drug is exposed to a much larger and diverse population, adverse events not seen during clinical trials often emerge in the first few years after a new product is on the market. PDUFA has fostered a dramatic reduction in product approval times, and the U.S. market is increasingly the country where drugs are first launched.

There is no evidence that drugs are being withdrawn from the market for safety reasons at a greater rate during the PDUFA era than prior to the enactment of this landmark legislation. In fact, the withdrawal rate for new drugs approved prior to PDUFA is identical to the rate of withdrawal for drugs approved since PDUFA was enacted (2.7 percent). However, the need to institute a more effective program of risk management for new drugs, and thereby ensure greater patient safety, is clearly warranted by the intrinsic limitations of drug development programs (particularly the size of clinical trials) and the reality that more drugs are launched for the first time in the U.S. Where risks can be effectively managed, we avoid the need to withdraw drugs that are highly beneficial to many patients, though harmful to some.

CONCLUSION

As you know, PDUFA II expires on September 30, 2002, and I want to emphasize again the importance of achieving a timely reauthorizion of this law. FDA is ready to work with you to accomplish this.

I have described the status of FDA's user fee account—Agency carryover balances will be exhausted by the end of the current fiscal year. If we are to sustain our record of accomplishment under PDUFA II, it is critical that the reauthorization occur without a gap between the expiration of the old law and the enactment of PDUFA III.

Timely reauthorization is a priority for the pharmaceutical industry, the American public, and the many talented staff at FDA that we rely upon to conduct human drug and biologic reviews. Retaining FDA's skilled employees is essential to the success of PDUFA III. Any hesitation or delay in the reauthorization of this program could trigger sudden 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 mission of FDA, and to the continued success of PDUFA. I am happy to answer questions you may have.

Mr. BILIRAKIS. Thank you very much, doctor. Dr. Crawford, when might we expect to receive in writing the goals performance letter, the agreement that was reached?

Mr. CRAWFORD. The goals performance letter is in draft, and I will ask Dr. Woodcock to comment to the extent that she is able to do so, when it might be delivered. However, I have seen it and have reviewed it, and I would say it is quite far along.

Mr. BILIRAKIS. All right. Before Dr. Woodcock speaks, I would like to say that I requested that FDA meet with the committee staff of minority and majority. They did so a couple of days ago.

Then of course there was a members meeting yesterday and Dr. Woodcock was there, with others. Dr. Zoon was there. I wanted to express our appreciation for that.

Dr. Woodcock, please tell us something good. You might also address the goals performance study, because as you heard members say here, before we go into a mark-up, we need to have that documentation to give you further cooperation.

Mr. CRAWFORD. I can address that. It is correct that it is being reviewed in the department. However, it is my understanding that both the FDA and the department share in the reasons for the delay.

It is very close to release, and I would say it is a matter of days. I communicated personally with the department yesterday and I expect that it will be released very soon indeed.

Mr. BILIRAKIS. Very soon? Can you give us an idea of what very soon is?

Mr. CRAWFORD. Days.

Mr. BILIRAKIS. Days? That's good. That is the goals performance study. Dr. Woodcock.

Ms. WOODCOCK. The letter, as Dr. Crawford said, is written—a draft is written and it must be reviewed by the original parties who have been negotiating this, as well as up the line.

We understand the need for urgency in getting this letter to you, and we will have it in a matter of weeks.

Mr. BILIRAKIS. Weeks?

Ms. WOODCOCK. Yes. We will make every effort to get it to you as soon as possible.

Mr. BILIRAKIS. The letter?

Ms. WOODCOCK. The letter, in a week or weeks.

Mr. BILIRAKIS. Week or weeks?

Ms. WOODCOCK. Yes.

Mr. BILIRAKIS. That is a little better.

Mr. CRAWFORD. It is a letter that is more like a novella. It is very large, and we want to make sure that it is right. But it should be—it is in very good shape now, I think, and it just needs to be reviewed by some more people.

Mr. BILIRAKIS. Okay. Well, please review. I understand sometimes that haste makes waste, but we need to have that documentation here as soon as we can so that we can continue.

We have an awful lot of things on our plate as you know, and as you heard, for example, prescription drugs and Medicare. We would like to get this thing on course.

Doctor, you have heard people up here state they are concerned that PDUFA may have resulted in a reduction in safety. PDUFA-2's trigger, is the requirement that PDUFA funds must augment and not replace the amount of reviews paid for by appropriated funds. A concern is that money is being diverted from other FDA centers, and that has been said here more than once.

Can you tell us what in the FDA-industry agreement, the performance goals agreement, will make this situation better? Has it

in fact been a concern? Has there been a reduction in terms of safety, efficiency, et cetera?

Mr. CRAWFORD. In reviewing the record of PDUFA, going back to the first one a number of years ago, over the past few days, I have personally been very interested in what the record is, and I believe it is safe to say that PDUFA-1 or PDUFA-2 have decreased risks.

The rate of withdrawal of drugs is essentially the same as it was before then. The agency is always extremely concerned about safety, and we will continue to be. With respect to what will be done in the new package to deal with the trigger, I am going to ask Dr. Woodcock once again to comment.

However, I know that that was a priority consideration and one that continues, and that I will follow up with that.

Ms. WOODCOCK. First, to set the record clear on one thing. We have increased our resources over the past 8 years devoted to drug safety within the agency. However, perhaps this has come at the expense of other programs.

The PDUFA trigger that you are talking about forces us to maybe overspend a little, because if we got down—if we went below the trigger, we could not collect user fees, and we would have to immediately lay off our staff.

We have tried in this agreement to build more flexibility into that, and that will allow us to be much closer, and not overspend in this program. Any time there is a decreasing resource environment overall for the FDA, some programs have to become smaller.

Mr. BILIRAKIS. Are we saying that PDUFA results in other programs being hurt?

Ms. WOODCOCK. If there is an overall decrease in appropriations to FDA, or the cost of living is not given to the program, then our number of staff must shrink. Just as if you were to give a raise, and you have 10 employees, and you gave a raise to all of them, and you didn't have any more revenues, you would have nine employees, and that is what has happened to the FDA over the last decade.

Mr. BILIRAKIS. In other words regardless of PDUFA, the same thing would have taken place because the money has not been there the way you would have liked to have had it?

Ms. WOODCOCK. But the trigger exacerbated that situation because we could not have nine employees in the user fee program. We had to maintain that program.

Mr. BILIRAKIS. My time is expired, but Dr. Crawford, very quickly you could compliment that.

Mr. CRAWFORD. I was just going to say that one of the things that Dr. Woodcock refers to is the fact that over the last few years that we have gotten raises for the FDA and we have had to absorb them from our budget.

This year, things are different as you well know, and we are grateful for that.

Mr. BILIRAKIS. All right. Thank you. Mr. Brown.

Mr. BROWN. Thank you, Mr. Chairman. Dr. Crawford, in light of what I have heard this morning, and especially what I will say as well on what we heard in the briefing yesterday from some of your fellow colleagues at the FDA, I am concerned about sort of the evolution of the FDA mission.

I hear some of your people calling industry its customer, and I heard yesterday talk and today about the launch of new products into the market. You have talked about a term that you learn in Marketing 101.

Industry uses the term launch, but the FDA using that term concerns me. Discussing the success of PDUFA, in terms of changes in the U.S. drug industry's market share, I guess I grew up thinking the FDA was there to protect safety and not to play a role in enhancing the U.S. market share.

And then coming yesterday and bragging about it with great enthusiasm, and coming in today and talking about that, and I just didn't know that that was the mission of this government agency to help U.S. companies' enhance market share.

Then I hear you quote Tufts, the Tufts' drug center or whatever it is called, which is always the group of experts that the drug industry both fires and then quotes for their drug studies.

It is mostly funded by them and I am just concerned about where the separation is. You are a regulatory body, and you are not a subsidiary of the drug industry. I am not accusing you of that.

But I just wondered where the separation is. I understand that one of the new agreements in the goals document is does it require the FDA to hire an outside consultant if the drug industry wants it to as long as criteria are set out in the agreement?

I understand the agreement requires the FDA to review its management practices because the industry is unhappy with these practices? I mean, I wonder where is the separation, and who is in control?

Is the FDA in control or is the industry that regulates in control? Then I hear that the stakeholders, when it comes to new drug reviews, and in a goals document, it includes industry and consumers.

But while the FDA held private negotiations with the industry, as I understand it the public forums were for patient and consumer groups. So the industry met behind closed doors, and the public meeting was with patients and consumers.

Then I read in the Congress Daily today that a landmark deal brokered by the prescription drug industry and the FDA, and it goes on and on, as if there are no other interested parties in this.

I realize that the industry funds PDUFA, but it is for a public purpose is what we were told 5 years ago and 10 years ago, and both public dollars and private dollars, fund new drug reviews.

Why were the stakeholders in this case, specifically why were they treated differently? Why the private negotiations with the industry, and then the public forum with the rest of us?

Mr. CRAWFORD. The FDA treads a tightwire of remaining correct, but aloof, in terms of its enforcement and in its consideration of the industry. Referring to the industry as a client or as a customer is sort of part of the new emphasis on stakeholder involvement.

And in the two public hearings that we held, where patient organizations and consumer groups came in, as you may recall, we had 28 different groups that came in to discuss their positions, and all made testimony.

And 23 of those were non-industry sources, and so that base was in fact covered. But I am sure they were——

Mr. BROWN. That was the public hearing, Dr. Crawford.

Mr. CRAWFORD. That's right.

Mr. BROWN. The private meetings, any of those 23 groups in there?

Mr. CRAWFORD. No. No. Now one of the——

Mr. BROWN. Then what am I missing here?

Mr. CRAWFORD. One of the reasons that it was necessary to meet with industry is because of a couple of things in my view. One is we have to be apprised of what the pipeline is; how many drugs are being developed, and what the needs are.

One of the goals, stated goals in the bill of PDUFA-1 was to speed up the drug approvals. And the second one as you know better than I was the same thing, plus performance standards that we would meet.

In order to set both of those, we needed a dialog with the industry. Many of the things that we discuss in these kinds of meetings are or have a lot to do with both the stock market and also the future of the industry, and how many things are there.

We have no way in FDA of knowing that until we have communication with industry.

Mr. BROWN. Well, perhaps then, Dr. Crawford, if those were public, then you might not be able to trot out that really cool chart of increasing and enhancing U.S. market share for the drug industry. Is that connected somehow?

Mr. CRAWFORD. Well, let me address that. Again, it is delicate, and I grant you that for sure. But the lesson that we have learned over the many years of the FDA Act is that each new generation of drugs is safer and more effective.

If we keep them off the market, or if we are not——

Mr. BROWN. Let me interrupt you there—I'm sorry—because I only have 5 minutes, and now I have no minutes. If each new generation is safer than a previous generation, why did you come in here a minute ago and brag about how you are taking no fewer percentage off the market. You are taking no more off the market than before.

In other words, PDUFA has worked well. But if these drugs are generally safer anyway, then there ought to be fewer recalls with these drugs that you approve. So in that way, PDUFA is not—PDUFA is working to get drugs to the market, and that is good for our consumers, and our patients, and our constituents.

But its primary object is safety, and it is failing on safety then if it is only the same rate as it was back when drugs weren't as safe as they were 10 years ago.

Mr. CRAWFORD. Well, we won't think it is failing on safety. There are more of them being approved, that's for sure, and Dr. Woodcock would like to make a comment.

Ms. WOODCOCK. There is a countervailing force, which is that more U.S. patients are the first in the world to be exposed to these drugs now. It used to be that Europeans, or Australians, or many people around the world, those populations, were the first to be exposed.

Mr. BROWN. And I might add in much higher numbers because of this extravagant launch in this huge use initially of these drugs,

in part because of the FDA's assistance with this launch in direct to consumer advertising. But go ahead, I'm sorry to interrupt.

Ms. WOODCOCK. Mr. Chairman, may I finish?

Mr. BILIRAKIS. Are you really sure?

Mr. BROWN. I'm sort of sorry, yes. Sorry.

Mr. BILIRAKIS. Please do it briefly, Dr. Woodcock.

Ms. WOODCOCK. Yes. Back when other populations were exposed, in those people the problems were discovered, and the drug was pulled off the market, and the application was withdrawn from the U.S. approval process before it got on the U.S. market.

Now that situation has totally changed, and that's why we feel that we need more of an emphasis on risk management.

Mr. BROWN. Okay. Thank you.

Mr. BILIRAKIS. Mr. Deal to inquire.

Mr. DEAL. Thank you, Mr. Chairman. My previously alluded to contact with Dr. Woodcock was quite the opposite. It was a complaint by a constituent of mine who had a drug pulled off the market, and they felt that it was a drug that needed to be there, and was considered lifesaving from their standpoint.

So there are points of view many times that the removal of drugs from the market is maybe overly zealous by some people's points of view. So I would simply make that point.

One of the concerns that we have heard expressed is that because of the so-called second trigger or the funding mechanism that funds are being diverted away from other functions within FDA.

Would you comment on that and is the agreement going to resolve that issue?

Mr. CRAWFORD. Well, of course it is our job to make sure that nothing that we are mandated to do gets compromised as a result of this or any other legislation. So we believe that PDUFA-3 will better address that problem.

We also as we mentioned a little bit ago, as long as we don't have to pay for the pay raise increases and some of these other things, we are more able to predict resources and do a better job.

And that issue has been dealt with very effectively in this Congress, and we are happy about that.

Mr. DEAL. Thank you. Since we have other members who have questions, I will waive the rest of my time, Mr. Chairman.

Mr. BILIRAKIS. Well, thank you. You caught me unawares here. Mr. Stupak.

Mr. STUPAK. Well, thank you. Dr. Crawford, I want to pick up where my friend, Sherrod Brown, left off. We talk about the mission statement of the FDA, which is safety and consumer protection is it not, or is it speed and more drugs?

Mr. CRAWFORD. It is not speed and more drugs, no.

Mr. STUPAK. Okay. On page eight of your testimony, you compare the withdrawal of pre-PDUFA and during PDUFA, and conclude that drug safety has not suffered because the withdrawal rates are basically the same 2.7 percent.

Out of those 12 drugs that have been withdrawn, only one was a life threatening drug, and the other 11 were for things like upset stomach and other things, correct?

Mr. CRAWFORD. Yes, I believe that is correct.

Mr. STUPAK. And you have over a thousand deaths, correct, with those 12 withdrawals?

Mr. CRAWFORD. We can——

Mr. STUPAK. To be exact, 1,012.

Mr. CRAWFORD. Well, we can submit that for the record. I am not prepared to say that.

[The following was received for the record:]

The Adverse Event Reporting System (AERS) maintained by the Center for Drug Evaluation and Research contains information on adverse events that may be associated with pharmaceutical drugs. AERS is a computerized information database designed to support the FDA's post-marketing safety surveillance program for all approved drug and therapeutic biologic products. The reports in AERS are evaluated by FDA clinical reviewers to detect safety signals and to monitor drug safety.

In evaluating AERS data, it is important to keep a number of considerations in mind. First, there is no certainty that the drug in question caused the reported deaths. A given death may actually have been due to an underlying disease process, use of a concomitant drug, or other unknown factors. The report rarely provides any basis for assessing whether the product caused the death. Second, since more than one health professional or other individual may file a report there may be duplicate reports filed on a single incident. Third, since many factors influence reporting for a particular drug, reliable comparisons between drugs cannot be made from this data. Fourth, AERS does not provide us with data on actual numbers of patients using the drugs in question. Therefore the ratio of deaths to the number of users cannot be calculated.

Finally, the decision to withdraw a product is complex and based on the totality of available evidence, including risks of potentially life-threatening adverse events, availability of alternative therapies, etc. The decision is not driven solely by reports of death, although such events are of most concern.

With these considerations in mind, the following list identifies the numbers of U.S. death reports in AERS from the time that a drug is marketed to the date of withdrawal, for drugs recently withdrawn from the market:

Pondimin-46
Redux-19
Seldane-354
Posicor-28
Hismanal-14
Duract-5
Raxar-3
Rezulin-188
Propulsid-288
Lotronex-7
Baycol-93.

Total number of death reports in AERS associated with these 11 products is 1,045.

Mr. STUPAK. Well, besides that, can you comment on the drug safety that are of concern the FDA that does not include product withdrawals?

By that I mean, provide us with the pre-PDUFA and PDUFA comparison of such post-market drug safety matters, such as warning letters, dear doctors letters, package inserts, black boxes, and other action taken by the FDA?

Those have dramatically increased under PDUFA, as opposed to pre-PDUFA, is that not correct Dr. CRAWFORD. I don't believe so. I am going to ask Dr. Zoon to answer your question from the standpoint of biologics, and then Dr. Woodcock to add whatever she would like, and they will give you a historical response, as well as an up-to-date response, and then I will follow through.

Ms. ZOON. Thank you. For biologics——

Mr. STUPAK. Excuse me. I don't want to spend my whole minutes talking by biologics. I just want to know about prescription drugs;

pre-PDUFA and post or during PDUFA. Do you have more black boxes, and more warning letters, more dear doctors?

[The following was received for the record:

A report to the Commissioner of FDA from the Task Force on Risk Management entitled, "Managing the Risks from Medical Product Use" was issued in May 1999. Appendix A of the enclosed report provides a comparison of post-approval risks for drugs and biological products approved before and after the implementation of PDUFA. This report was also provided in its entirety in response to questions for the record.

Ms. ZOON. The withdrawal rate for biologics is actually less post-PDUFA than pre-PDUFA. The issue of the warning letters and other labeling instances we would be happy to get back to you.

Mr. STUPAK. So you don't have an answer? Okay.

Ms. ZOON. I don't have the numbers right here with me.

Mr. STUPAK. Well, let me ask you this. In the goals and performance letter that we are going to get either in a week or weeks, whatever it might be, what mechanism is there in the performance letter to make sure that these performance and goals are actually met by the pharmaceutical industry?

Or are we going to have a situation like PDUFA-2, where you do your post-marketing, and 90 percent of it isn't done, and here you want to reauthorize PDUFA-3, and 90 percent of the goals were met in PDUFA-2?

Mr. CRAWFORD. Well, we believe that this goals letter does represent the newest science, and we feel that we will do a far better job because of that. One of the things that we have come to deal with is risk management and also the problems with the peri-approval process.

Just as the product is about to enter the market, as we have talked earlier about direct to consumer advertising, the label itself, and all these sorts of things, which make a lot of difference.

In other words, the product has been reviewed, and it is getting close to labeling and market entry, and we are going to emphasize that a great deal more. It helps us, I think, to think in terms of pre-market activities, and also to think of the approval and review activities, and then the peri-approvals time.

The time was when the agency quite frankly approved the drugs, and allowed them on the market, and then unless we got adverse event reports, adverse reactions, we didn't do very much.

Mr. STUPAK. Doctor, with all due respect, how are you going to enforce it? What is the enforcement mechanisms? Why are we here? You have no subpoena power, and you can't fine anybody, and you can't subpoena anybody.

For Serzone, we have been waiting for over 6 years for the pediatric exclusivity study. Over 6 years. They got a 6 month extension, and we are still waiting for that. What power do you have to get the pharmaceutical company to give you that study?

And in another drug, in accutane, you have been waiting since 1985 for the raw data from the manufacture. Tell me how you are going to enforce that?

Mr. CRAWFORD. Well, we have certain enforcement activities.

Mr. STUPAK. Tell me one.

Mr. CRAWFORD. I am going to ask Dr. Woodcock, because I don't know what happened in the 1994 thing, if I may be permitted to do so, and then I will follow up.

Ms. WOODCOCK. Well, first of all, under the new—your first question, under this agreement, under a proposal that we have, we will be substantially increasing our post-marketing staff and our risk management staff. That was your first question. Your second question——

Mr. STUPAK. So you have more staff, and that doesn't mean enforcement. You have more staff. Go ahead.

Ms. WOODCOCK. Currently for many of the—as you know, for many of the post-marketing problems that we encounter, our major authority and major step that we can take is to pull the drug off the market.

Mr. STUPAK. How many have you ever pulled when you didn't get a study or report that you have been demanding? Serzone is still there, and still pediatric exclusivity, and granted by the way, and should not be used for minors, but it is still out there.

Doctors are still prescribing, and they still don't know after 6 years what it is safe or not for adolescents. That is not pulled. Accutane, 1985, and we are still waiting for the raw material, and there have been repeated requests of the manufacturer. That has not been pulled.

Have you ever pulled a drug because they have not complied with your request for studies for data, for information, that is critical to the safety of a drug? Have you ever done that?

Ms. WOODCOCK. I think only when that was coupled with a safety problem, a severe safety problem that warranted pulling it off.

Mr. STUPAK. So there has to be something more or there is no enforcement?

Mr. BILIRAKIS. The gentleman's time has expired.

Mr. STUPAK. Thank you, Mr. Chairman.

Mr. CRAWFORD. Mr. Burr.

Mr. BURR. Thank you, Mr. Chairman. Dr. Crawford, and Dr. Woodcock, and Dr. Zoon, welcome. Thank you for all the work that you do. I apologize, Mr. Chairman, that I wasn't here for opening statements, but I would like to reinforce something that I understand that the chairman said in his opening statement.

I think that the FDA has done an extremely good job of meeting with the industry and trying to put together a goals letter. I very much would like to see that in a matter of days, signed, and a copy delivered, and I think that weeks is not an option here. And I hope that you will take that back——

Mr. BILIRAKIS. If the gentleman would yield. As significant as it is to get this thing reauthorized before the time expires, I don't know how I in good conscience can set up a mark-up unless we have the goals performance agreement in writing, as well as the study. This should be presented to us in adequate time.

Please proceed, Mr. Burr.

Mr. BURR. I thank the chairman for that. In an effort to try to keep our efforts focused, as your efforts are, and that is to a very valuable tool in the process of processing applications, and bringing new drugs to the market in a timely fashion, I hope that as we move through this mark-up period that my colleagues on this sub-

committee, as well as the full committee and the House, understand the importance of this reauthorization.

Sure, we can chicken out and stick it on the appropriations bill later this year, and not talk about some of the things that are legitimate in this debate, but at the end of the day reauthorization of user fees mean that we bring potential new products to the marketplace that have a tremendous quality of life effect on the individuals that are waiting for these drugs.

And, yes, we potentially bring down long term health care costs because we eliminate the in-patient stays. And I think that is the real work of this committee as we try to sort out the health care marketplace in the future.

Let me ask you if I could relative to the goal sheet. I understand that a risk management program was agreed to by the industry and the FDA that will effectively double the number of FTEs dedicated to drug and biologic safety. What type of advance is this for the American people and does the industry support the FDA's risk management plan?

Mr. CRAWFORD. Yes. We believe that they do and they will. This is an extension of what I was talking about, this peri-approval process. We are going to devote more effort, and more resources of other types to that, not the least of which will be electronic information technology.

And as I mentioned earlier, I believe that in FDA's history there was a time when we sort of put the drug out there and we didn't worry that much about it. And that time is changing, and we recognize that this kind of surveillance, once a product is on the market, is a very real and sacred trust that we have. And we will be working hard on that.

Mr. BURR. Dr. Crawford, in your testimony, I think you alluded to the fact that there was a—I call it a disparity, a difference between the review and approval times for drugs, versus biologics. Why does that disparity exist between the two centers?

Mr. CRAWFORD. Well, I will give a general response and then ask Dr. Zoon if she has comments. Drugs, as you well know, are chemical entities, and many of them are similar to drugs that have already existed, and that simply have another molecule on them or something like that.

And we are able to have a body of information, and we have had even the most advanced drugs like anti-cancer drugs and antibiotics now for many, many years. So we have a residue or body of understanding about them that enables us to review them more carefully.

With biologics, many of them are bioengineered drugs of one sort or another, and they are also—there is gene therapy that is covered in biologics, and this is something new for us, and we have to do it very, very carefully indeed. And it just takes a little more time.

Ms. ZOON. There are a number of issues, particular speaking about biologic supports and solicitation of getting to the marketplace for consumers, safe and effective therapies as quickly as possible.

And in fact the Center for Biologics has met all of its PDUFA goals. All of them were exceeded, all of its PDUFA goals. The issue then comes down to what is the reason why the times are longer.

And there is multiple reasons, and it is not all related to one single issue.

One deals as Dr. Crawford said with the complexity of biological products, and many of these are cutting edge technologies, and a lot of the issues with large complex molecules need to be dealt with, and things can go wrong with them.

Sometimes in the manufacturing and the ability to be able to make these products consistently, and other times they deal with manufacturing and facility issues, and being able to prepare them in a way to ensure that they meet GMP compliance.

And then other issues surrounding the clinical efficacy data, and safety data with many of these ground breaking products. We tried to work very hard with the companies to work out these issues.

I think in the context in the future of PDUFA-3 that there will be more support for those interactions, and to try to deal with those problems proactively by having additional resources to facilitate those issues.

Mr. BILIRAKIS. The gentleman's time has expired.

Mr. BURR. I thank you for that progress and I thank you for the time, Mr. Chairman.

Mr. BILIRAKIS. Again, that is why we are very anxious to see the results of all of your negotiations and your discussions. Ms. Eshoo.

Ms. ESHOO. Thank you, Mr. Chairman, and I want to thank you for what you said just a few moments ago, and that is how important it is to have the side agreement come to us sooner rather than later.

And I have to tell you that if you want to see this thing move, weeks is not good. Weeks means more than a month, and what we have to do—this Congress is not going to bump up to Christmas. There are elections this year, and so we are going to be getting out in October.

So we have a very limited timeframe here, and so thank you, Mr. Chairman, for setting that down as a priority. It is an important one. I want to pursue with Dr. Zoon if I might the whole issue of outcomes. How do you explain the differences—well, first of all, to set the stage.

Most of the companies that we are dealing with relative to the special protocol reviews and that are small. And so they really need help navigating this process. So in many ways they are more agency reliant than others are, than the big guys are. How do you explain the differences in special protocol reviews?

It is 129 for the CDER, which for my colleagues if the scrambled letters don't make that much sense to you, that is the Center for Drug Evaluation and Research. It is 129 for the CDER and one for the Center for Biologic Evaluation, and Research.

And given that these reviews as I said are supposed to help the smaller companies negotiate the complicated process, wouldn't you expect the reverse? I would expect the reverse to be true. Can you enlighten us about this?

Ms. ZOON. Well, I can say that I don't know all the answers. I think there are some explanations at least that I can give, and perhaps our colleagues when they have a chance can also elaborate on that.

Many of the issues of concerns to biologic manufacturers are generally arranged during our planned meetings that have been scheduled under the PDUFA program.

So one does not actually need to utilize the special protocol in order to discuss important clinical trial design issues or manufacturing issues, or other items of importance in product development.

So many of those issues are addressed during those meeting, and the meeting minutes are generated and agreed to.

Ms. ESHOO. Well, let me just interject something though. As we listen to constituents and what they say, I am always mindful that if you only pick up on what one person says, and put a multiplier on it, you may be causing a boomerang on a hundred others.

But there is a common thread of complaint in this area. So if this were being taken care of in the consultation, or what did you just refer to what it is?

Ms. ZOON. Our meetings?

Ms. ESHOO. Your meetings. Why would there be these complaints? I mean, if it is already being taken care of, and it is a lopsided number. Maybe you can't give the answer, and maybe subsequent panels will speak to it, panel members. But it is an area that is a rub.

Are you pleased with it, and do you have something from inside the agency where you are trying to beef this up and improve upon this outcome?

Ms. ZOON. Well, I think the answer is that if in fact this particular vehicle under PDUFA-2 was made available for everyone—the question is how many people actually know about it and utilize it to the extent perhaps they may wish to, or want to, in other areas.

Ms. ESHOO. Let me ask you this. What is the agency doing to proactive if you think that people don't know, and you see it as being highly workable and a problem solving arena?

I have a sense that there is a shortcoming here, and I am not trying to pick on you or find something. In our review of when we reauthorize this, it is always about making something good even better.

So I am mindful of that and I think that this is an area where there is a shortcoming, and the approval times that CBER—I think that seriously when you look at the numbers, they seriously lag behind those at the CDER.

So that is up to the agency to tell us why this is so. These are the numbers that you have created, and that's why I raised them.

Mr. CRAWFORD. If I could respond. These meetings are as Dr. Zoon indicated optional, but the reason that we—we need to find out the reason that they are not taking advantage of them. So there is some sort of shortcoming.

Ms. ESHOO. But have you raised them from inside the agency to take a look at it, or is it the Congress through these hearings weighing in that is making you aware of it?

Are we both doing it at the same time, or have you looked at it, looked at this number, 129-to-1, and said, all right, now we see that this isn't all that it should be, and this is what we are doing.

Or is this news to you today, or is it something that you have not had time to take a look at, even though you are aware that the numbers aren't so great?

Mr. CRAWFORD. This is not new to us. It is something that I have not had time to take a look at, but I will, and I appreciate that.

Ms. ESHOO. Is there any news about the appointment of the Commissioners at the FDA?

Mr. BILIRAKIS. Why don't you ask Dr. Crawford very briefly Ms. ESHOO. Dr. Crawford, do you want to comment on that? You know, I raised that because—I know that people are thinking I am raising it because of political sensitivity or whatever.

The FDA is one of the most important Federal Agencies in our entire Nation. My constituents bank on the FDA protecting them. I mean, they feel very strongly about it, and I know in the past when there were attacks and whatever, they said, look, don't destroy or take the whole thing down.

And so for an agency to be—well, I shouldn't say rudderless, but not to have a person at the top I think is why I raise it. What can you tell us?

Mr. BILIRAKIS. Very briefly, Dr. Crawford.

Mr. CRAWFORD. Unfortunately, I can't tell you anything, and I will be honest with you.

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

Mr. BILIRAKIS. Dr. Zoon, do you have something to add to that?

Ms. ZOON. The only thing, and just to further address one of the issues is that one of our thoughts is, and we actually are going to be doing some proactive outreach to make sure that people understand what PDUFA offers to them in a outreach program as part of our center initiatives.

Because I think we saw the numbers, and we are trying to understand them, but we think one thing we can do is do more outreach to make sure that people understand the options open to them.

Mr. BILIRAKIS. All right. Thank you, doctor.

Ms. ESHOO. Thank you, Mr. Chairman.

Mr. BILIRAKIS. Dr. Norwood to inquire.

Mr. NORWOOD. Thank you, Mr. Chairman, and I do thank all the panelists for being here, particularly Dr. Crawford, who is a former professor at the University of Georgia, and at Georgetown University, a couple of my favorite universities out there.

So welcome one and all. The questions have all been good it seems to me for once, and we are all sort of on the same page, but I want you to tell it to me. Do you believe PDUFA-3 needs to be preauthorized?

Mr. CRAWFORD. I do believe it needs to be authorized. It is very important for the public health of this country.

Mr. NORWOOD. It is very important for the public health of this country, and I would say that in some ways that it is pretty important for the FDA, too, wouldn't you agree with that?

Mr. CRAWFORD. Absolutely, yes, sir.

Mr. NORWOOD. Well, since you were down in Georgia long enough, we can have some straight talk. Dr. Crawford, we need that performance goal letter by 5 p.m. Monday. There is absolutely

no reason that all of us are going to work next weekend, and you put your people to work, too.

If you want to have this thing authorized, you get that letter to the chairman. We have problems, too. Now, get it done. And if you can't get it done on Monday by 5 p.m., tell me right now why; or just better yet tell me you will get it done.

Mr. CRAWFORD. It pains me to beat around the bush here, but——

Mr. NORWOOD. Please don't. Please don't do that.

Mr. CRAWFORD. But we will make every effort to get it as soon as we possibly can, and that is——

Mr. NORWOOD. No, that is not an answer. It is not reasonable for you not to answer the question. If you can't get it by 5 p.m. Monday, when? The date. And then make it work. This is critical.

Mr. CRAWFORD. Okay. Well, you know, until we get into it, we can't really say the exact date, but I hear you.

Mr. NORWOOD. Yes, you can. You set the date and make them go to it. The chairman will not authorize this without that document.

Mr. CRAWFORD. We understand that, and we will get to work on it, and that is a promise.

Mr. NORWOOD. Can anybody tell me if 5 p.m. on Monday is okay?

Mr. CRAWFORD. I think I am the one, and I do, too. I do know that. Okay. I hear you.

Mr. NORWOOD. Well, I don't know how to say this any other way, except to say that you are not answering the question, and it is a good thing that we are friends, and all of that, but you need to answer the question.

You need to commit yourself to when the chairman will have the documents so we know what to do, because we all want to look at the document, and we hope then from that that we can reauthorize a critical issue. Now, set the darn time, and work, and make it happen.

Mr. CRAWFORD. We will surprise you.

Mr. NORWOOD. Well, I have a feeling that we will surprise you back if you don't surprise the subcommittee.

Mr. CRAWFORD. I am well aware of that, yes.

Mr. NORWOOD. Mr. Chairman, I think I am through.

Mr. BILIRAKIS. We have a series of votes. I had hoped that we could finish up with Dr. Crawford before we left, but there is just no way that we can do it. I think we are going to have to break.

Please, let's get back just as soon as we cast that second vote. I think there is two of them, and let's finish up. Thank you.

[Brief recess.]

Mr. BILIRAKIS. Mr. Bryant to inquire of Dr. Crawford.

Mr. BRYANT. Thank you, Mr. Chairman, and Dr. Crawford, welcome. I just have a few follow-up questions, three to be precise, and so I will try to squeeze those in about 5 minutes, and so if you could take and consider that when you answer.

I have been in and out, but I know that the FDA has done some studies in regard to the issue that perhaps some have been about rushing these reviews, and in some respects compromising safety.

I don't know how much you have talked about those studies, but I would like to have those, if reasonable, attached to your testimony. Is that a very large study, or is it feasible?

Mr. CRAWFORD. No, we can give you some information on that and attach it without exception.

[The following was received for the record:]

The Office of Inspector General (OIG) of the Department of Health and Human Services is evaluating the efficiency and effectiveness of the review process for new drug applications under PDUFA II. We understand that the OIG is in the drafting stages of their report.

Mr. BRYANT. Can you give me a bottom line?

Mr. CRAWFORD. Yes. The bottom line is that since PDUFA-1 went into effect, the number of drugs that have to be recalled because of safety concerns has not changed, and although more drugs are being approved, no higher percentage are having these kinds of difficulties.

Mr. BRYANT. You were about to answer a question earlier on from someone, and you were cutoff a little bit, and you started out if you can remember this that if you keep the drug off the market, and you were kind of cutoff at that point.

I assume that this has some connection with the impact of PDUFA on making drugs and biologics more available to the American consumer? Could you explain that for me?

Mr. CRAWFORD. Yes. What I was referring to was that each new generation of drugs that FDA has regulated has genuinely been safer and even more effective than the previous generation.

So when a new drug, which is a breakthrough entity that has real prospects for improving public health in the country comes along, it is incumbent upon us in my view to review it as fast and as accurately as we possibly can so that it can get on the market and begin improving the public health of this country.

We can't compromise the safety and efficacy requirements that we have, but if it isn't introduced expeditiously, and it hasn't been too many years ago when it took 4 or 5 years to do what we are doing now in about 6 months.

And people did suffer as a result of that, and so we have done a variety of things, like PDUFA, and even some other initiatives to try to be sure that the drug is safe, and be sure it is effective, and then if it has the promise that many of these do, try to get it on the market, or try to get it approved as soon as we possibly can.

Mr. BRYANT. My last question is has PDUFA had any effect on pharmaceutical research and development?

Mr. CRAWFORD. Well, actually, if you go back and look, and all of us have been briefed on this, one of the goals was to send a signal to the pharmaceutical industry, and the biologics industry, that the FDA is shaping up its approval process.

We are changing as a result of PDUFA, and rather than getting credit for turning down drugs, we are going to get credit for approving drugs correctly.

And that message being sent to the pharmaceutical industry was intended to spur innovation and development of these new drugs, particularly those for diseases that no drug existed for, and we think by and large that it has worked.

Mr. BRYANT. I have no other questions, but just one comment just in follow-up to Mr. Norwood. I think you received his message clearly, and coming from an arena of law here I had to negotiate quite a bit, and I understand the situation that you are in with this letter, and there is some give and take on this, but if one side is under a deadline, usually they are at a disadvantage.

But I think in this case that neither side—I think that both sides have a real interest in getting this done, and so even though you are here and we are talking to you, I would send that message out clearly to those in the audience that represent the other side, and who very clearly have a strong interest in this bill being reauthorized that we really need agreement as quickly as possible, and maybe even as soon as next Monday.

But it would help us in that regard. So I think that all the parties agree that we need to have this done. Thank you, and I yield back my time.

Mr. BILIRAKIS. I would expect that there are an awful lot of representatives here from quote, the other side, who have gotten that message. Mr. Waxman to inquire.

Mr. WAXMAN. Thank you very much, Mr. Chairman. Dr. Crawford, rapid drug approval has put an extra burden on FDA to watch for unexpected safety problems after marketing.

The FDA no longer has the luxury of a lengthy review period to detect safety issues before approval, nor does it have the advantage of watching the European experience with a drug before it is marketed here.

At the same time the FDA's post-market surveillance system is seriously flawed. It is based on voluntary reporting from health care professionals, and I understand that the FDA estimates that it hears of less than 1 percent of serious adverse reactions.

And while the FDA allocates over 2,000 FTEs to premarket reviews of new drugs, it has been able to assign less than 5 percent of that number to post-market safety monitoring.

I am concerned that the FDA's current post-market surveillance system is not up to the challenge posed by rapid drug approvals. What changes in FDA's post-market surveillance program are needed to run an effective program, and will the amount of money the industry has put forward pay for the needed changes?

Mr. CRAWFORD. That is one of the things that I am very concerned about, and have been briefed on by Dr. Woodcock and her staff. And I would if I may like to ask her to give the bottom line of those briefings.

Ms. WOODCOCK. That is a complex question you are asking. The recommendations that we have arrived at would actually double the size of the review staff in drug safety at the agency, and that would be a tremendous boost.

However, there are many drugs, of course, that are generic, that are off patent, that have safety problems. Most of the drugs on the market have not been newly approved, and as you know, my feeling is that drug safety is a broad issue, and it does not pertain to the first year or so after a drug is approved.

It pertains to all drugs that are on the market. We find problems years, sometimes decades, after a drug is on the market.

Mr. WAXMAN. Well, you mentioned that this funding from user fees will double the staff of post-marketing, but I understand that is over a 5 year period.

Ms. WOODCOCK. Correct.

Mr. WAXMAN. Just tell us in your best professional judgment what would FDA need to have in place to do a post-market surveillance program that will accomplish what we would like to see ideally to assure the public about the safety of drugs that are on the market?

Ms. WOODCOCK. For drugs, we need money for access to data bases, and the linked health care data bases that exist now, and the health care organizations that link adverse reactions to prescriptions, and outcomes, we need the money to do studies so that when health problems are detected or suspected with drugs, we can go out and confirm or evaluate whether or not these are real, and if so, what to do about them.

Mr. WAXMAN. I assume the money that will be provided in this agreement with the industry will not be sufficient to do what ought to be done for a post-marketing surveillance program.

Ms. WOODCOCK. In my judgment that is true, but that many of these drugs are not new drugs.

Mr. WAXMAN. How much money and how many staff people in your best professional judgment would be needed to do a good post-marketing surveillance program? You might want to get it for the record.

Mr. CRAWFORD. Yeah, I think that is a good idea. Can we submit that for the record?

Mr. WAXMAN. Yes, please. I understand in this agreement with the industry that it authorizes the FDA to use a portion of the user fees to gain approximately a hundred new FTEs devoted to post-market safety over the next 5 years.

And while it is a good start, and welcome change, I am concerned that though there is apparently nothing explicit in the agreement about the number of FTEs that FDA can add to the post-market surveillance program.

Instead, the only explicit part of the agreement is a goal that is set for premarket review. And I would like to know how we in Congress can be sure that the fees currently earmarked for post-market safety will in fact be used for that purpose.

For example, if in a given year the FDA does not have sufficient resources to meet its performance goals, which again are only for pre-market approvals, what will stop the agency from taking resources from the post-market safety program to help meet performance goals for faster approvals?

Ms. WOODCOCK. We issue a report to Congress yearly, both a performance report and a financial report. We would expect that the yearly reports issued under this new program would have a line item for how many dollars, and how many FTEs are devoted in drug safety from user fees.

Mr. WAXMAN. Well, I guess what I want to try to focus on is that the agreement, which could be the basis for legislation, spells out a performance goal for premarket reviews, and no performance goals for post-market safety activities.

Don't you guarantee that post-market safety will always be sacrificed in order to meet pre-market review deadlines? And is pre-market review speed more important than post-market safety evaluation from a public health point of view. I think we would both say no.

But can we be assured that we are not going to find ourselves in a position where that money is going to be used for pre-market instead of post-market if you fail to meet those performance standards?

Ms. WOODCOCK. We have viewed it as an obligation to use the money as it has been intended under the user fee program, and that is laid out in the reports that we give to Congress. And I don't think that we would change the money around.

Mr. WAXMAN. And will the people hired with user fee money be allowed to work on non-PDUFA-3 drugs?

Ms. WOODCOCK. Could I answer that, because it is complicated?

Mr. WAXMAN. Yes, sure.

Ms. WOODCOCK. It is a level of effort arrangement. We don't have people with a star on their head saying user fee people, and non-user fee people. So we would have to devote a certain level of effort to the PDUFA-3 drugs, if that makes sense to you.

But it would not be by individual, individually. Individuals would work on whatever was appropriate.

Mr. WAXMAN. Can I ask just one last question, Mr. Chairman?

Mr. BILIRAKIS. Yes, but just briefly.

Mr. WAXMAN. My last question is this. I am concerned about the fact that we have direct to consumer advertising by the pharmaceutical manufacturers, and the FDA has a role to make sure that it is not false and misleading.

I also understand that the FDA has very, very, little resources to accomplish that goal. Perhaps for the record you could tell us what you would need if you were actually going to do the job that you have the power to do, but not the resources to do, to supervise these consumer ads to be sure that they are not false and misleading.

Mr. CRAWFORD. May we submit that analysis for the record also?

Mr. WAXMAN. And please submit the answers to my questions about optimal staff and budget, in terms of your best professional judgment, and not what is approved by every politician around, but your professional judgment.

Mr. CRAWFORD. Thank you, sir.

[The following was received for the record:]

The Division of Drug Marketing and Advertising (DDMAC) in the Center for Drug Evaluation and Research (CDER) is responsible for the regulation of prescription drug advertising. This Division currently has assigned 39 full-time equivalents (FTEs) positions. While DDMAC has worked to maximize its productivity and is currently undergoing a reorganization that is designed to further improve its efficiency and effectiveness, the current staffing is not adequate to keep pace with the rapidly increasing number of professional and direct-to-consumer advertisements for prescription drugs. It is estimated that CDER would need approximately 35 additional FTEs and supporting operating funds to fully staff the advertising review program.

Currently, the Center for Biologic Evaluation and Research (CBER) has 4 FTEs to review all advertising and promotional labeling materials submitted. In order to adequately assess these materials and bring timely enforcement actions, a large increase in staff would be required. Based on the projected number of submissions for FY2003, and conservative estimates of man-hours needed to review these submissions, 30 additional review FTEs would be required. Additional management and

support staff would also be needed, for a total of 38 FTEs at a cost of $5,130,000.00. An additional $550,000 would be required for IT upgrade and support of a tracking system. This would result in a total requirement of $5,680,000.00.

Mr. BILIRAKIS. We will be submitting, of course, a number of questions to you. There are people here who have sat around all morning long, and haven't had the opportunity to inquire of you, Dr. Crawford.

Per usual, you will be responding to those in a timely fashion. That being the case, we are going to finally excuse you and express our appreciation to you, and Dr. Zoon, and Dr. Woodcock, for the long delays and sitting in the chair as long as you have.

Mr. CRAWFORD. Thank you very much.

Mr. BILIRAKIS. Thank you very much. Again, help us to help those who need to be helped.

Mr. CRAWFORD. We shall do that.

Mr. BILIRAKIS. Thank you. Panel Number 2 will consist of Dr. Timothy R. Franson, Vice President of Clinical Research and Regulatory Affairs, U.S. Eli Lilly Research Laboratories; Dr. Alastair J. J. Wood, Assistant Vice Chancellor for Research, Professor of Medicine, and Professor of Pharmacology, at Vanderbilt University School of Medicine; and Dr. Mary Pendergast, Executive Vice President of Elan Corporation.

Welcome to all three of you. We can start off with Dr. Franson. If you would, please. We are setting the clock at 5 minutes. Your written statement, of course, is a part of the record.

We would hope that you would supplement or compliment it, and let's do the best that we can.

Dr. Franson, please proceed.

STATEMENTS OF TIMOTHY R. FRANSON, VICE PRESIDENT OF CLINICAL RESEARCH AND REGULATORY AFFAIRS, U.S. ELI LILLY RESEARCH LABORATORIES; ALASTAIR J.J. WOOD, ASSISTANT VICE CHANCELLOR FOR RESEARCH, VANDERBILT UNIVERSITY SCHOOL OF MEDICINE; AND MARY K. PENDERGAST, EXECUTIVE VICE PRESIDENT, ELAN CORPORATION

Mr. FRANSON. Thank you very much. Chairman Bilirakis, Ranking Member Brown, and members of the subcommittee, thank you for the opportunity to discuss the reauthorization of PDUFA.

My name is Tim Franson, and I am a physician, a pharmacist, and Vice President of Clinical Research and Regulatory Affairs at Eli Lilly and Company. And I am representing the views of the Pharmaceutical Research and Manufacturers of America, PhRMA.

Very few legislative initiatives have been as effective and successful as PDUFA. The user fee program was created while keeping two overriding and principled goals in mind. There must be no real or perceived paying for a drug approval, and patient access to new treatments must be expedited.

The results of the program are tangible. Since enactment of the program in 1992, the FDA has approved 712 drugs, and 198 of these being priority reviews, which have had a remarkable positive impact on patients.

It is critical to note that the user fees are designed to be added to FDA appropriated base funds. Congress wisely added two trig-

gers to assure that the FDA could not collect user fees unless the base line appropriation for FDA was preserved, and the necessary funds within the appropriations were spent on drug review in the full sense.

The public health advantages of PDUFA cannot be overstated. Patient access to new, safe, and effective medicines has been expedited. Prior to the initial passage of the legislation, drug reviews at FDA took on average over 30 months.

The review time has been cut in half over the past 9 years that the program has been in effect. The FDA is now approving new, life-saving therapies before other regulatory agencies in the world, giving American patients first access to these important medicines.

There is improved, appropriate communication between the FDA and the companies developing these new drugs, and thus facilitating the decisionmaking process. And according to FDA statistics, the law has had no effect on market withdrawal rate, which has remained at 2.7 percent, both pre-and-post-PDUFA.

Clearly, this program is an excellent example of how to structure a successful working relationship between the regulator and the regulated without compromising safety and efficacy standards.

The integrity of the program is in its simplicity; incremental resources for FDA and measurable performance goals. These goals have been kept out of the statute and dealt with in a side-letter from the Secretary of HHS to Congress.

The statute is explicit about the use of user fee funds, and they can only be used for the process for the review of human drug applications. The retention of this limitation is critical to the proper scope of PDUFA.

It focuses the additive resources on the activities that best serve the broad public health goal of the law, the prompt review of important new drugs.

PDUFA-1 focused solely on the drug review process, and PDUFA-2 focused on improving interactions during the clinical drug development phase. As we look forward to extending this program, we identified several key objectives.

Continuing to assure a sufficient financial base for FDA. Incorporating the most current information technology into the review process. Exploring new concepts to bring additional efficiencies to the process.

Improving performance management, and continuing to assure that the safety of new drugs is of the highest priority. The FDA has proposed a risk management program in which the agency would gain additional resources to evaluate risk management plans associated with new products.

These will address questions of what may occur as products reached to a larger number of patients in the first 2 to 3 years of marketing, the time in which a vast majority of risks are identified.

Additional user fees will be allocated for the risk management program, and this will complement the extensive programs that the FDA and PhRMA member companies have in place to monitor post-market safety of new drugs.

In closing, I want to acknowledge the over 1,000 professionals at FDA, who are a large part of the success of this program, and who are dedicated to doing their job to the highest standards.

PhRMA hopes that Congress will act to reauthorize this program, assuring these employees of the shared commitment of all parties to continue the program for another 5 years, and to assure continued, timely flow of new therapeutic advances to waiting patients.

Thank you, and I will be happy to answer any questions that members of the committee may have.

[The prepared statement of Timothy R. Franson follows:]

PREPARED STATEMENT OF TIMOTHY R. FRANSON, VICE PRESIDENT, CLINICAL RESEARCH AND REGULATORY AFFAIRS, ELI LILLY & COMPANY ON BEHALF OF THE PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA

Mr. Chairman and Members of the Subcommittee, I'm pleased to be here on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA) to present its views on the reauthorization of the Prescription Drug User Fee Act (PDUFA). PhRMA represents the nation's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to live longer, healthier, and more productive lives. Investing more than $30 billion in 2001 to discover and develop new medicines, PhRMA companies are leading the way in the search for cures. Right now, our companies have some 30,000 researchers working on more than 1,000 potential new medicines. We want patients to have access to safe and effective medicines as soon as possible. That's why we're here today.

As members of this Subcommittee well know, opportunities to make a real societal difference through legislation are unique and special. PDUFA, enacted in September 1992, was clearly a central piece of legislation that has affected the lives of many American citizens who needed prompt access to important new medicines. The Energy and Commerce Committee played a critical role at that time and the Commerce Committee was key again in 1997 when PDUFA was reauthorized as part of the Food and Drug Administration Modernization Act. As the members of this Subcommittee are aware, PDUFA expires at the end of this federal fiscal year. Prompt reauthorization is critical to all the stakeholders: to industry, which seeks *to maintain* timely review; to the FDA, which anticipates gaining important additional resources; and most of all, to the American public, who await new advances that our industry is developing to treat their diseases from cancer and AIDS to Alzheimer's and diabetes.

The public health benefits of PDUFA cannot be overstated. Patient access to new safe and effective medicines has been expedited. Prior to the initial passage of the legislation in 1992, drug reviews at FDA took on average over 30 months. The review time has been cut in half over the past nine years that the program has been in effect. FDA is now approving new life-saving therapies before other regulatory agencies in the world, giving American patients first access to these important medicines. There is improved appropriate communication between FDA and the companies developing these new drugs. This leads to a greater and timelier exchange of information, facilitating the decision-making process. Finally, this program is a clear example of how to structure a successful working relationship between the regulator and regulated without compromising standards.

The results of this program are tangible. One need only look at the number of drugs and biologics approved over the past nine years. FDA has approved 712 drugs; 198 of these were priority reviews. Among the examples of new treatments that American patients have access to are:

(1) *Gleevec*—A drug approved for the treatment of chronic myeloid leukemia, which is a rare and deadly disease that affects some 25,000 Americans. A priority drug, it was approved in just over two months.

(2) *Xigris*—A drug approved for the treatment of adults hospitalized with severe sepsis that are at a high risk of dying. Prior to the approval of Xigris, about 1,000 people died of this condition every single day. A priority drug, it was approved in under 10 months.

(3) *Trisenox*—A drug approved for the treatment of leukemia (acute promyleocytic leukemia) in patients who have not responded to, or have relapsed following all trans-retinoic acid and anthracycline-based chemotherapy. A priority drug, it was approved in six months.

(4) *Mylotarg*—A drug approved for the treatment of a certain type of leukemia (CD33 positive acute myeloid leukemia) for patients 60 years or older who have relapsed for the first time and are not suitable candidates for the standard but poorly

tolerated cytotoxic therapy. A priority and orphan drug, it was approved in about seven months.

(5) *Zyvox*—A drug approved for the treatment of bloodstream infection, hospital-acquired pneumonia, and community-acquired pneumonia. A priority drug, it was approved in six months.

The concept of a user fee program to augment FDA resources was first proposed by the Agency. The lengthy time of drug reviews was attributed to the lack of adequate resources, a view put forth by the FDA and agreed to by the pharmaceutical industry. A distinct need for supplemental resources on top of those appropriated by Congress was established with one principal goal: there must be no real or perceived "paying for a drug approval." Over the past nine years this goal has been met. Although performance goals were established in both PDUFA-1 and PDUFA-2, these were kept out of the statute and dealt with in a side letter from the Secretary of HHS to Congress. Thus, the PDUFA law itself is rather simple, covering the fee structure, how fees can be collected, and what they can be used for.

It is critical to note that the user fees are designed to be additive to the FDA appropriated base funds. Congress, in its wisdom, added two "triggers" to assure that FDA could not collect user fees unless there was a baseline appropriation for all of FDA and the necessary funds within the full appropriation were spent on drug review activities. Collectively the two "triggers" emphasize the ongoing public responsibility to provide FDA with adequate resources to carry out its mission to advance the public health.

PDUFA-1 focused solely on the drug review process, reducing the time to FDA action to six months for priority drugs and twelve months for standard drugs. FDA also agreed to process the backlog of pending applications within the first two years of the program. Both goals were accomplished.

While PDUFA-1 focused on FDA review time, PhRMA stressed that the FDA review of an application, while significant, is only a fractional portion of the whole drug development time that was taking as long as 12 years. As the pharmaceutical industry looked toward the first reauthorization of PDUFA in 1997, proposals were offered to the FDA that would improve interactions during the clinical development phase of drug development with the hope that improvements in this lengthy process (6-8 years) could be realized with the same degree of success that occurred with the FDA review phase. Agreement was reached on a set of metrics that has made such interactions more predictable. In addition, PDUFA-2 incorporated processes for resolving disputes, assessing special protocols, providing prompt feedback when sponsors submit information in response to a clinical hold, and simplifying the action letter that the sponsor receives following the review of an application. Collectively, these enhancements are beginning to improve the drug development process.

As PhRMA began preparing for the PDUFA-3 reauthorization, we recognized that this is a sound program that works and works well. The integrity of the program is its simplicity: measurable performance goals in return for the added incremental resources for FDA. The statute is explicit about the use of user fee funds; they can only be used for the "process for the review of human drug applications." The retention of this limitation is critical to the proper scope of PDUFA; it focuses the additive resources on the activities that best serve the broad public health goal of the law, the prompt review of important new drugs. While no less important, the broad array of other FDA regulatory activities that deal with a host of post-market issues are best funded out of the federally appropriated budget. PhRMA recognizes the critical role of these activities and the necessity for full funding of the Food and Drug Administration.

One critical issue that surfaced back in 1992 was whether the nature of the proposed legislation constituted a "tax" on industry. It was argued at that time, successfully, that the program would not be a tax, but rather a fee for service. Thus, Congress avoided a difficult jurisdictional decision as to whether referral to the House Ways and Means and the Senate Finance Committees would be required. PhRMA would urge the Subcommittee to preserve the current language in the statute to insure that PDUFA continues to meet the above-mentioned process definition. In this manner, PhRMA hopes that Congressional jurisdiction will remain clear and unambiguous.

The goals for the program over the next five years are straightforward. We must preserve the significant process improvements that have been made over the past nine years of PDUFA. PhRMA consistently has complimented the FDA for meeting every established performance goal, in most cases well ahead of schedule. Interactions between the FDA and sponsors of new medicines have never been better. The predictability of the regulatory process provides a degree of certainty to companies' drug development programs.

There are some key aspects of the proposed PDUFA-3 program that are worth discussion.

- We need to continue to assure a sufficient financial base that preserves the current services and achievements made during the first two cycles of PDUFA. The current FDA budget that fully funded the Agency's current cost of living increase was of great assistance in meeting this goal.
- We must continue to move toward incorporating the most current Information Technology (IT) into the review process. Over the five years of PDUFA-2, industry has provided over $80 million of user fees to upgrade the IT infrastructure of both the Drugs and Biologics Centers. By the end of this fiscal year, FDA will be in a position to receive all regulatory submissions in electronic format. This includes not only the New Drug Application, but also the large amount of information that is required during the clinical development process, the annual reports that are required of all approved drugs, and the reports of adverse drug reactions. Industry is willing to continue this level of funding and add extra funds toward targeted programs. We must remember that FDA is responsible for managing large amounts of information and this ongoing IT initiative is critical to the Agency's function.
- We need to continue to explore new review concepts that will bring additional efficiencies to the process. PhRMA has proposed to pilot a "cumulative marketing application" in PDUFA-3. Rather than waiting until the full application is complete, FDA would begin to review defined modules of the submission, as they are finished. This "building" of a reviewed NDA may lead to marked improvements in the way drugs are reviewed.
- We need to develop a workload adjuster that reflects all of the activities of the new drug review process, rather than just the completed NDA submission. FDA allocates user fee resources to the review of efficacy and manufacturing supplements as well as all of the interactions with sponsors during the clinical development time period. During PDUFA-2, workload was calculated only on the basis of fee-paying applications. By a rough estimate this represents only about 40% of the net review burden of the Agency. If the number of these applications dip, as it has in the last couple of years, FDA's ability to carry out all of its responsibilities will be hampered by insufficient additional resources.
- PhRMA and the FDA have been in agreement that the safety of new drugs must continue to be one of the highest priorities in the development and approval process. To this end, we have been in frequent discussions with other PDUFA stakeholders to improve this function. We all acknowledge that drugs are not without risks. The basic premise of drug development is managing the benefit/risk relationship. Additional information on the safety of drugs emerges constantly, particularly in early use following approval. PhRMA companies already dedicate significant resources, both personnel and money, to pre- and post-approval safety vigilance activities. While there has been no increase in the rate of drug withdrawals during PDUFA compared to pre-PDUFA periods, the FDA has proposed a risk management program in which the agency would gain additional resources for the purpose of evaluating risk management plans associated with new products, and to address questions of what will occur as products reach larger numbers of patients in the first 2 to 3 years of marketing—the time in which the vast majority of risks are identified. Additional user fees will be allocated for the risk management program.
- We should allocate a modest proportion of PDUFA funds for improving performance management. By implementing "good review management principles," FDA can bring consistency throughout the review divisions that are located within both CDER and CBER. Secondly, as the PDUFA program enters its third cycle, PhRMA believes that this is an appropriate time for a major management review focusing on process review and analysis within the two Centers. This review should be comprehensive, involving a thorough analysis of IT utilization, review management, and activity cost. The resultant process map should enable FDA to make far greater use of its principal resource, people power.

Finally, we must not lose sight of the dedicated employees at the Food and Drug Administration who are a large part of the success of this program. User fees now support well over 1000 men and women who are dedicated to doing their job to the highest professional standards. PhRMA believes that Congress needs to act with all due speed to reauthorize this program, assuring these employees of the shared commitment of all parties to continue the program for another five years and the continued timely flow of new therapeutic advances to waiting patients.

Mr. BILIRAKIS. Thank you very much, Mr. Franson.

Dr. Wood.

STATEMENT OF ALASTAIR J.J. WOOD

Mr. WOOD. Mr. Chairman, Representatives, and Ladies and Gentlemen, thank you also for giving me the opportunity to testify today. As you already heard, I am Alastair Wood from Vanderbilt University, where I am Assistant Vice Chancellor, and Professor of Medicine, and Professor of Pharmacology.

But I am also the drug therapy editor of the New England Journal Of Medicine. Prescription drug user fees have provided the FDA with additional resources to allow effective therapies to reach patients faster.

The program has clearly been a great success and has achieved its goal. And with respect to that, I would like to highlight a number of points from my written testimony that addressed the future under PDUFA.

We are at a time when the potential for innovative drug development has never been greater. While that innovative potential is enormously exciting, it will put extraordinarily new demands on the FDA.

If only a percentage of the genes discovered by the Human Genome Project reveal new drug targets, this will provide thousands of new drug classes, and I am not just talking about new drugs. New drug classes never before seen.

Facilitating such innovative therapies to market will require paradigm shifts in the way that we think about evaluation of safety and efficacy. Some of these new challenges are already apparent.

The old models used to demonstrate efficacy may not be optimal for the therapies of the future. Drugs are being developed, for example, to enhance immune function in HIV AIDS.

The reduction in viral load, which is the current standard measure of efficacy, may not be the optimal efficacy end point for such drugs. In the cancer area, a number of novel therapeutical strategies are in development.

Here, too, the old measures of effectiveness based simply on reduction in tumor size may need reevaluating. Pharmacogenetics, defined as the effect of genetics on drug response, has the potential to identify patients whose particular genetic backgrounds made them either more likely to respond to therapy, or put them at particular risk from side effects.

If it is an early stage in the drug development process, we can identify patients who, because of their genetic make-up, respond to a drug. And then by including only such patients in clinical trials, we could substantially reduce the number of patients that we need to study.

The agency needs to work with industry to identify the issues related to the use of these more efficient trial designs, and ensure that their use does not result in overly restrictive labeling.

Questions have been raised this morning about the effects of PDUFA on drug safety. The issue is framed sometimes in different ways. Sometimes the question has been posed are we approving drugs too quickly.

I think the answer is clearly no. We are not approving drugs too quickly. In fact, I would go further and say that there is no intuitive reason to imagine that slowing the approval process will enhance safety.

Drugs are not like wines; they don't improve with keeping. An additional way that the question has been posed is are we withdrawing more drugs because of safety concerns since PDUFA.

Again, the data do not appear to support that conclusion. Another question that has been raised is how should PDUFA influence post-marketing surveillance? As someone has already said, the answer is complicated.

First, it is worth saying that effective post-marketing surveillance is not and should not be the enemy of industry. Poorly performed post-marketing surveillance may result in the needless removal, as we have already, of safe and effective drugs from the market on the basis of invalid data.

Fortunately, the information technology revolution is about to radically change the way physicians prescribe drugs. At Vanderbilt Medical Center, all physician's orders for in-patients must now be entered by computer.

Dosage, interaction risks, et cetera, are checked automatically at the time of prescribing, and the results fed back to the physician before direct transmission of the prescription to the pharmacy.

The implications for improved patient safety are obvious and compelling, but there are also substantial opportunities for post-marketing surveillance.

We will have access to complete data sets on prescriptions and outcomes, with positive implications for the drug approval process. The greater our confidence in the post-approval data, the earlier and faster we should be able to approve drugs.

These prescribing systems are moving forward rapidly, and the FDA needs immediately to be a player in the development of such systems.

In summary the upcoming challenges to the FDA are substantial. These challenges can only be met if the agency has the resources to hire and retain the quality scientific staff it needs.

The salaries of FDA scientists need to be maintain parity with academia, and should be tied to the NIH salary cap. If we are to fulfill our hopes for novel therapies in the future, it is essential that the FDA has the increased resources it needs to participate as a full and credible scientific partner.

User fees alone cannot be expected to provide the required increases in resources. Additional public funds are required to adequately fund this critical public health agency. Mr. Chairman, thank you for giving me the opportunity to present these views.

[The prepared statement of Alastair J.J. Wood follows:]

PREPARED STATEMENT OF ALASTAIR J.J. WOOD, ASSISTANT VICE CHANCELLOR, VANDERBILT UNIVERSITY SCHOOL OF MEDICINE

Mr. Chairman, Representatives, Ladies and Gentlemen, I am Alastair Wood from Vanderbilt University where I am Assistant Vice Chancellor, Professor of Medicine and Professor of Pharmacology. I have spent my entire professional life studying and writing about drugs. I have served on FDA advisory committees and have been the Drug Therapy Editor of The New England Journal of Medicine for over a decade.

The purpose of the Prescription Drug User Fee Act was to provide the FDA with the additional resources it needed to allow faster review of NDAs and therefore have effective therapies reach our patients faster. The program has clearly been a great success and has achieved that goal. The success of the program and the occasion of its reauthorization provide an opportunity to look into the future to determine

what actions are required to ensure that we can continue to further enhance the drug approval process.

There has probably never been a time in drug development at which the opportunities were greater. While these opportunities are exciting they will also put extraordinary new demands on the FDA. It has been estimated that all of the drugs currently on the market act on only 500 different molecular targets. If only a percentage of the genes discovered by the Human Genome Project reveal new drug targets this will provide thousands of new Drug Classes—Not just new Drugs—But completely new drug classes never seen before. Facilitating such innovative therapies to market will require, not more of the same but paradigm shifts in the way we think about evaluation of safety and efficacy.

Some of these new challenges are already apparent. The old models used and demanded to demonstrate efficacy may not be optimal in the future. New approaches from biotechnology drug development are already posing new and unanswered regulatory questions. Drugs are being developed to enhance immune function in HIV/Aids—Reduction in viral load—the current standard measure of efficacy in HIV patients may be inappropriate for such drugs. In the cancer area drugs are in development to reduce the occurrence of metastatic cancer, to reduce blood vessel supply to tumors, to increase drug entry into cancer cells, while yet others will target the cell signaling processes that are deranged in cancer cells. Here too the old models of effectiveness based simply on reduction in tumor size may need re-evaluating. The development of such new approaches will require all of the stakeholders—Industry, regulators, academics and patients working together to define robust, relevant and measurable end points for the clinical trials of the future.

Pharmacogenetics—The effects of genetics on drug response has considerable potential to enhance drug investigation and the approval process. It will allow us to identify patients whose particular genetic backgrounds either make them more likely to respond to therapy or put them at particular risk from side effects. Such genetic information is already being used to optimize drug dosage in the treatment of childhood leukemia. Of particular relevance to our discussion today is how this pharmacogenetic information could improve the drug approval process. If at an early stage in the drug development process we can identify patients who, because of their genetic makeup, respond to a drug, then by including only such patients in our clinical trials we could substantially reduce the number of patients who have to be entered into the pivotal trials required for drug approval. Conversely the ability to identify patients at particular risk of developing side effects from a drug and the exclusion of such patients from treatment or studies will also affect the risk benefit profile of such a drug. Drugs, which might otherwise be considered too toxic for widespread use, may be safely developed if we can exclude the patients at risk of toxicity. The regulatory issues are enormous and will again require substantial effort on the part of all the stakeholders. The Agency needs to work with industry to identify the issues related to the use of these more efficient trial designs and ensure that their use does not result in restrictive labeling.

Concerns have been raised about the effects of PDUFA on drug safety. The issue has been framed in various ways.

Sometimes the question is posed—"Are we approving drugs too quickly?" I think the answer is clearly—No—we are not approving drugs too quickly in fact I would go further and say that there is no intuitive reason to imagine that slowing the approval process will enhance safety but such delays do prevent effective therapy reaching our patients. Delay has no inherent safety value, but may simply reflect indecision or lack of intellectual confidence.

An additional way that the question is posed is "Are we withdrawing more drugs since PDUFA?" Again the data do not appear to support that conclusion.

Another question that has been raised is "How should PDUFA influence post marketing surveillance?" The answer is complicated. But first it is worth saying that effective post marketing surveillance is not, and should not, be the enemy of industry. Inadequate post marketing surveillance will fail to identify drugs with unacceptable risk/benefit profiles. However just as importantly poorly performed post marketing surveillance is also dangerous because it may result in the needless removal of safe and effective drugs from the market on the basis of invalid data. Neither of these outcomes is acceptable. In addition the greater our confidence in the ability to generate quality post marketing data the greater should be our ability to approve drugs earlier.

Fortunately changes in information technology may assist us. Doctors still prescribe drugs much as they have done for 2,000 years. With little assistance, they write out a prescription from memory (sometimes still in Latin!), give the prescription to their patient who carries it to a pharmacist, who tries to read it and dispense the correct drug. That process is about to change rapidly. At Vanderbilt Medical

Center all physicians' orders for inpatients must now be entered by computer. Dosage, interaction risks etc are checked automatically at the time of prescription before direct transmission of the prescription to the pharmacy. Such systems will soon also be available and widely used in the outpatient setting. The implications for improved patient safety are obvious and compelling. However the introduction of such computerized prescribing systems also have huge implications for post marketing surveillance—For the first time we will have access to complete data sets on prescriptions and outcomes. Again I see these innovations as having positive implications for the drug approval process. The greater our confidence in the post approval data the earlier and faster we should be able to approve drugs and use them to treat our patients. Issues of privacy need to be dealt with but these systems are moving forward rapidly and the FDA needs to be integrated into such systems now so that the information can be used to push back the time to drug approval.

I list these examples of the exciting new challenges and opportunities to you to emphasize that in the immediate future we are going to have to undertake considerable rethinking of our approach to the demonstration of drug safety and efficacy. Such innovative thinking will need to involve all of the constituencies—industry, regulators, legislators, academics and patients and will require considerable effort from us all. Reducing the time to drug approval does not depend solely on the review time for an NDA it also requires efficient trial design and execution and enhanced sponsor confidence that innovations in trial design and in definition of end points will be accepted at the time of NDA review. The strategy to speed drug approval needs to extend across the entire life cycle of development and use of a drug and therefore demands investment not just in the review process itself but also in developing and maintaining excellence in the pre and post approval process. The speed of scientific change and development of new knowledge requires a strategy to ensure that FDA's scientific staff maintains cutting edge scientific skills. Such strategies will require funding which will not come from user fees, yet the benefits should flow directly to better reviews and more efficient drug development strategies. Drugs can be developed faster if only meaningful high quality studies are demanded and required to be performed.

Thus as we think about PDUFA reauthorization the opportunities offered by drugs to relieve the diseases that have plagued mankind are enormous. The challenges to the FDA to develop the new paradigms required will be substantial. These innovations will only be forthcoming if the agency has the resources to hire and retain the quality scientific staff it needs. The FDA competes with both industry and academia for such scientific talent. The salaries of FDA Scientists need to maintain parity with academia and should be tied to the NIH salary cap. If we are to fulfill our hopes for novel therapies in the future it is essential that the FDA has the increased resources it needs to participate as a full and credible scientific partner. User fees alone cannot be expected to provide the required increase in resources. Additional public funds are required to adequately fund this critical public health agency.

Mr. Chairman thank you for giving me the opportunity to present my views today.

Mr. BILIRAKIS. Thank you, Mr. Wood.

Ms. Pendergast.

STATEMENT OF MARY K. PENDERGAST

Ms. PENDERGAST. Mr. Chairman and members of the subcommittee, I am Mary Pendergast, Executive Vice President of Elan Pharmaseuticals, a member of the biotechnology industry organization.

Thank you for letting me testify on behalf of BIO. Our message today is simple and it echoes what you have heard before. The Prescription Drug User Fee Act is an extraordinarily successful piece of legislation, and we are here to urge you to renew the program for another 5 years, quickly, and without taking on other issues.

The additional resources provided to the Food and Drug Administration through user fees have facilitated FDA's review of new biotech therapies, many of which are life-saving, without compromising the agency's ability to make sound and scientific medical and regulatory decisions.

In fact, the proportion of drugs removed from the market for safety reasons has not changed because of the user fee program.

Yet, because safety is a paramount concern of industry, consumers, and FDA, we are ready to provide the FDA with additional resources to work with companies, physicians in and academic medicines, such as Dr. Wood, and consumer groups, to improve our understanding of the risks imposed by drugs and biologicals.

And to find new methods to reduce those risks, companies will also work with the FDA to develop specific risk management plans for products that will be coming on to the market in the next 5 years.

These new risk management efforts will buildupon the FDA's already considerable powers to give the public an added margin of safety. We also hope that the user fee resources will be used to respond to a problem we see in the FDA's implementation of the user fee program.

There appears to be significant differences among FDA review divisions, as well as one center to the other, in both their review processes, and the timeframes for their application reviews.

We want to understand the reasons for these differences, and we want to find ways to address them and hopefully reduce or eliminate them. So we hope that the FDA will study how it is conducting reviews now, devote both management attention and user fee resources to improve their review processes.

And look at ways to enhance communication with companies during reviews, and to minimize the inconsistencies between the Center for Biologics and the Center for Drugs.

Finally, because we recognize that biotechnology products are often novel and complex, we propose that FDA spend new and additional user fees that we are willing to put forward to bolster its access to the expertise crucial to the review of biotechnology products.

We hope that user fees will be used when necessary to hire outside experts to help determine how a company could demonstrate safety and effectiveness. These experts would be selected by the FDA and screened by the agency, and the agency of course would have final decisionmaking authority.

Thank you for the opportunity to present BIO's views at this meeting. We look forward to working with the subcommittee and the committee to reauthorize this important program.

[The prepared statement of Mary K. Pendergast follows:]

PREPARED STATEMENT OF MARY K. PENDERGAST, EXECUTIVE VICE PRESIDENT, ELAN CORPORATION

Mr. Chairman and Members of the Subcommittee, I am Mary K. Pendergast, Executive Vice President for Government Affairs at Elan Pharmaceuticals Management Corporation. I am pleased to be here today on behalf of the Biotechnology Industry Organization (BIO), to talk with you about the Prescription Drug User Fee Program and to urge the Subcommittee and the Congress to reauthorize this program, which expires at the end of this fiscal year.

The Biotechnology Industry Organization, BIO, represents more than 1000 biotechnology companies, academic institutions, and state biotechnology centers in all 50 U.S. States. BIO members are involved in the research and development of health-care, agricultural, and environmental biotechnology products. The companies BIO represents range from large, multinational corporations to much smaller, emerging companies. Since its establishment in 1993, BIO has worked with this Subcommittee on a variety of issues, including the one we discuss today—the prod-

uct review and approval process at the Food and Drug Administration (FDA). BIO was active during congressional deliberations in 1996 and 1997 that led to the Food and Drug Administration Modernization Act and, importantly, to the reauthorization of the Prescription Drug User Fee Act (PDUFA).

I want to begin by thanking this Subcommittee and its Members for your work over nearly ten years in creating and then continuing the user fee program for drugs and biologics. You were there at the beginning, with the first user fee bill sponsored by Mr. Dingell, Mr. Waxman, and others on the Energy and Commerce Committee; you were there five years later at the first reauthorization, with legislation sponsored by you, Mr. Chairman, Mr. Burr, Mr. Greenwood, and others; and here you are again. We greatly appreciate your support of this critical program.

I also want to reiterate what already has been said here today: the Prescription Drug User Fee Act has been and remains an extraordinarily successful piece of legislation. Prior to enactment of PDUFA, FDA was often behind other nations of the world in approving new pharmaceutical products. What Congress and FDA repeatedly heard was that American patients waited while patients elsewhere had access to important new therapies. The drug and biologic user fee program reversed that scenario. Because of the additional funding made possible through the user fee program, the United States now leads the world, rather than following it. Today, FDA is the world's leading regulatory agency, not only in terms of the quality and safety of the products it approves for marketing, but also in terms of ensuring that new products are available to patients as soon as possible.

For BIO, two key measures of the success of PDUFA I were, first, whether the law has facilitated FDA's review and approval of new products without compromising the agency's ability to make sound scientific, medical, and regulatory decisions and, second, whether the law worked for patients.

By both of these measures, the initial user fee program succeeded. User fees enhanced FDA's resources so the agency could hire additional medical and scientific reviewers and function more effectively in its review of new products. And that was accomplished without a diminution in safety. Anyone who has worked with FDA knows they are now, as they always have been, the toughest regulators in the world. User fees have not changed that, nor has reducing average review times changed the proportion of products withdrawn from the market for safety reasons.

Thus, when the time came to reauthorize the program in 1997, there was a keen recognition that we were seeing something unusual—a newly established program that had worked the way it was expected to work—one that a wide variety of stakeholders were praising. PDUFA II also has been successful by many measures. Communication between FDA and application sponsors has continued to improve, leading to better applications and more effective use of scientific resources in making decisions. And, most importantly, the health of patients has improved through access to new products like Herceptin for metastatic breast cancer, Zevulin for non-Hodgkins lymphoma, Enbrel—the first disease modifying agent for rheumatoid arthritis, Xigris—the first therapy for life-threatening sepsis, and Synagis to protect newborns from potentially fatal infections.

Mr. Chairman, as the Subcommittee moves forward with its work on reauthorizing this program for a second time, we know you will build on its successes. In particular, we are hopeful that in the next five years of the user fee program, while FDA maintains the strong standards it now requires, we will see enhanced efforts regarding product safety. This enhanced product safety program—FDA's risk management proposal—will be supported by user fees. With these additional user fees, FDA's risk management program will hopefully prove to be an even better pharmacovigilance system than that which already exists in the United States.

We also hope that you will recognize that positive results do not necessarily equate with perfection. As we have looked more deeply into the statistics regarding what has occurred over the last four years, we have recognized that some modifications in how the program is implemented may be in order and may improve on successes already achieved. The things we are looking at do not involve ways in which we think the law needs to be changed. Indeed, it is BIO's view that minor, largely technical, changes in the law may be called for, but that fundamentally this statute works well and should remain essentially intact. We also hope that this important legislation will not become a magnet or a train to which many unrelated provisions will be attached.

Reports of PDUFA progress generally deal in averages across the agency, and often do not separate these averages to allow examination of whether different components of the agency are fulfilling the goals of PDUFA at the same level. This kind of sub-analysis is of great importance to the biotechnology industry, which often brings to FDA products that are complex, unique, and the outgrowth of emerging science. We are keenly interested in how the process for reviewing these bio-

technology products—which are the primary preserve of the Center for Biologics Evaluation and Research (CBER)—and the time frames in which they are reviewed, tracks the review process and time frames for other pharmaceutical products.

When BIO has examined the data, we have seen what appear to be significant differences among review divisions, as well as from one center to another, in both the review processes and the time frames for application reviews. We want to understand the reasons for these differences and we want to find ways to address and even reduce or eliminate them.

To achieve this goal, BIO is proposing some modifications that we hope will enhance the FDA's review processes over the next five years. These proposals would not require any change in the legislation, nor in the standards for approval, but would be achieved within FDA through the agency's modification of some of its existing processes.

First, BIO hopes to be able, through the user fee annual reporting mechanisms already in place, to see more clearly where there are differences among review divisions and between the two reviewing centers, the Center for Drug Evaluation and Research (CDER) and CBER, in terms of meeting the various goals of the user fee program.

Second, BIO wants to see a more structured allocation of user fee resources to activities related to review process improvements, as well as greater involvement by officials in the Office of the Commissioner in evaluating these review processes, looking for opportunities for improvements and efficiency gains, and taking steps to implement them. Therefore, we propose that a small portion of user fee resources be specifically dedicated to review process performance improvement activities and that these resources and activities be overseen by the Office of the Commissioner.

Third, we hope to improve further the level of communication between FDA and sponsors during the first review cycle. As you know, Mr. Chairman, the goal of PDUFA is for FDA to complete its review of an application in a designated period of time—six months for a so-called priority application, and ten months for a non-priority, or standard application. FDA's action on an application may be a letter to the sponsor requesting more data or information, a letter stating that the application is disapproved, or a letter stating that the application is approved. If FDA asks for more information, the sponsor generally provides the information to the agency, and then FDA enters into a second cycle of review, which can take several additional months. After this, third, fourth, and even fifth review cycles may be needed, depending on what additional information FDA requests after each of its reviews. Our review of data in FDA's reports to Congress, and information provided on the agency's web site, shows quite striking differences between the centers in regard to their ability to reach final decisions within one review cycle.

With reviews that both FDA and sponsors believe have worked well, one of the common themes we have found is early and on-going communication. Another factor that influences review processes—and, consequently, review times—is inconsistency among divisions and between centers in review practices. To address both of these factors—communication and consistency—we propose that FDA look at ways to enhance communication and to minimize inconsistency through the development, articulation, and implementation among divisions and between centers of effective review practices. We believe such sharing of good practices will go a long way to resolving differences among divisions and between the centers and will also contribute to greater efficiency of review across the board.

Finally, BIO would like to encourage FDA to use another mechanism for obtaining expert advice on cutting edge issues. BIO recognizes that biotechnology products are often novel and complex so that only a small number of research scientists and medical specialists have the expertise to understand how the products' development should proceed. Specifically, it is often the case with these products that appropriate design of the clinical trials needed for product approval is more difficult than it would be with more well-understood science. The resources CBER currently devotes to its laboratory-based, scientific studies do not address sufficiently this expertise shortage. We propose that FDA initiate a mechanism whereby an outside expert could be brought in to a meeting between the product sponsor and the FDA to assist the sponsor and the agency in deciding how best to achieve the data needed to demonstrate safety and effectiveness for the product. Such an expert would, of course, be selected by the FDA and, as is currently the case, would be screened by FDA, to ensure no conflicts of interest and no breach of the confidentiality of proprietary information. We propose that a company be provided one opportunity for such an expert consultation, so this would not become overly burdensome for the agency. As is always the case, the recommendations or views of any consultant would be advisory to the FDA, which would remain the final decision-maker.

In summary, BIO shares with FDA the goal of reauthorizing PDUFA in a way that not merely maintains but strengthens the FDA's drug and biologic review programs. We believe that the user fee program has provided, and will continue to provide, the agency the user fee resources it needs to do its work. Indeed, we propose that under PDUFA III, FDA receive a substantial infusion of new resources. But we also hope in the course of PDUFA III to achieve a better handle on review process efficiency, especially as it relates to biotechnology products, so we can look forward to even more enthusiastic support for the program reauthorization in the year 2007.

Mr. Chairman, we share the belief that timing is critical in this reauthorization process. FDA must, because of federal personnel rules, initiate a Reduction in Force (RIF) unless the agency has the legislative authority to continue providing the salaries and expenses that are derived from user fees. Notices of the possibility of such a RIF must be sent to FDA employees no later than August 1, 2002, 60 days before the end of the fiscal year and detailed plans for any RIF must be developed months earlier than that. BIO urges you, Mr. Chairman, and the Subcommittee and Committee, to act with all appropriate speed to ensure the future of this program.

Mr. Chairman, thank you for the opportunity to present BIO's views at this hearing. BIO looks forward to working with the Subcommittee and the Committee in your continuing role as the initiators and overseers of this important and highly successful program. This program has improved and even saved patients' lives, and has made the U.S. biotechnology industry the most productive in the world.

I would be happy to answer any questions you may have.

Mr. BILIRAKIS. Thank you.

Well, Dr. Wood, and I will say Ms. Pendergast, how does the FDA compare to other countries in terms of regulating drugs; the efficacy, the safety, et cetera?

Mr. WOOD. I think this is undoubtedly the gold standard internationally and for drug regulation. It is the gold standard in lots of ways, both in terms of scientific expertise, in terms of the rigor with which drugs are reviewed.

But also importantly I think, and something that we tend not to think about it in this country, the openness with which that process operates. In many other countries the process is much more secretive and advisory committees being held in the open, and individuals' views being exposed to open criticism in the public, and is not characteristic of the approach taken in many other countries.

So I think we have an excellent system, but that doesn't mean that we can't do better, and we can't improve many of these things, but most countries I think would view this as one to which they would aim rather than the opposite.

Mr. BILIRAKIS. Thank you. Ms. Pendergast.

Ms. PENDERGAST. I share Dr. Woods' views. The FDA is and remains the gold standard for the rest of the world, and I think this is especially true with regard to safety.

I feel as though the FDA has been unfairly criticized for its safety record.

I think we need to remember that in the United States that only approximately a tenth of the drugs are pulled from the market as they are pulled in other countries. So I think that while it is true that drugs do get pulled from the market from time to time, the FDA has an enviable record compared to the regulators in the rest of the world.

Mr. BILIRAKIS. Concerns have been raised by members of the panel that PDUFA, or at least this is the way that I interpreted their statements, that PDUFA may have hurt the quality of FDA, particularly safety, and maybe shifting from what was done previously to PDUFA because of the fees coming in.

Do you have any comments regarding that, Ms. Pendergast?

Ms. PENDERGAST. I do not think that the prescription drug user fee program has impacted safety. I think the data shows that a lesser percentage of drugs have been pulled from the market now than before.

I think we have studied twice as many patients before putting drugs on the market than we did before the prescription drug user fee program began, and I think we have a solid safety base upon which the FDA can make decisions.

So I do not think that the user fee program, which has given the FDA additional resources, has impacted adversely on safety.

Mr. BILIRAKIS. Thank you. Dr. Wood you are an academic. I would say you probably don't have any axes to grind, I am not insinuating that anybody does, about your opinion.

Mr. WOOD. Yes, I think that one of the things that we need to do is we need to look at the safety of a drug throughout its life cycle, and one of the things that we have focused on today, I guess, has been PDUFA, which really focuses on the narrow part of the life cycle of a drug, the time during which an NDA, or a new drug application is being considered and approved.

But really we need to—and of course that is the part for which PDUFA fees are available—we really need to focus on the breadth of the entire life history of the drug before the NDA is filed during the appropriate—ensuring that the appropriate studies are done, but not excessive studies are done.

And that requires an appropriate interaction to industry, and FDA, and others. But also in the post-market, what I have heard is the concerns about the post-marketing surveillance being inadequate, and whether that should be wrapped up, and we can talk about that, I guess, later.

Mr. BILIRAKIS. Dr. Wood, I want to go into one area very quickly. These recommendations that you have just made in terms of details, I understand that you touched on that in your statement.

If you have any specific recommendations regarding these areas, if you could give that to us in writing so that we can take them all into consideration, and the sooner the better obviously, so that we can do this on a timely basis, and consider them.

Post-market surveillance. All of us agree that it is a necessary function of the FDA. I don't know that anybody has disagreed with that. Just comment, in terms of the user fees, on whether user fees will be adequate for that, and if not, should it be accomplished with appropriated dollars.

Mr. WOOD. Well, I have not seen the specifics as you have either.

Mr. BILIRAKIS. Well, we haven't either.

Mr. WOOD. But the stories that are circulating include statements which may not be correct. That the ability to use these user fees will be restricted to some period after approval, and 2 years for drugs without a black box warning, and 3 years for drugs with a black box warning.

That seems to be inappropriate, and if——

Mr. BILIRAKIS. Inappropriate?

Mr. WOOD. Inappropriate, given that for the first 6 months of a drug's approval you usually have no data. It just does not come in that quickly, unless something really bad is happening.

And then after that, and in the last 6 months of that 2 year period, people obviously are going to be distracted and thinking about other things. So you are really looking at a window of a year in there, and that seems inadequate, and seems like an inappropriate restriction to put on it.

There are two problems in the post-marketing surveillance area. One is for drugs where we already know the side effect before the drug goes on the market. And the second one is where we are looking for novel side effects that have not been recognized prior to the drug going on the market.

And these are different problems, and that need different solutions. In the first case, where we already know about the side effects before the drug goes on the market, you are talking about a management issue.

How do you educate doctors and others appropriately to use these drugs, and we have done a relatively poor job of that. It is not the FDA's fault entirely. It is people like me perhaps that are to blame for that, academics and physicians, who perhaps have not gotten that word out.

But uniformly when we have made labeling changes to drugs, these labeling changes have not been widely incorporated into physicians' practices. So where we have information on side effects, we are not able to translate that readily into action.

In the other setting where we are looking if you like and sort of drilling for oil, and we are looking for unexpected side effects that have never been described before, that is difficult, because we are better at identifying side effects that have already been recognized.

For example, it is easy for a physician when a patient develops a rash to say that might be the antibiotic that you were taking, and to make that connection. It is much harder for a physician to make a connection between some adverse event that may be drug related, but has not been previously described.

Now, that's where the opportunity of a computerized prescribing really opens up tremendous opportunities. Quite quickly, physicians are going to start prescribing drugs on their Palm Pilots. And they are going to be prescribing the drugs like that, and then sending it to the pharmacy.

We still prescribe drugs very much like we have done for the last 2,000 years. You know, we get our pen out of our pocket, and we get a bit of paper, and we try and remember the dosage, and we try and remember the drug, and all the stuff that goes with that.

And we write it down, sometimes in Latin still on a bit of paper, and the patient carries that in their hand to a pharmacy, and the pharmacy tries to read my writing, and translate that and give the patient the drug.

And that really has been virtually unchanged in 2,000 years. Clearly that is going to change dramatically, and has already changed in the in-patient setting at Vanderbilt, and will change dramatically over the next 2 years.

This is not going to take long, and we need to have the agency incorporated into these systems at the get-go for two reasons. One is that we can use these systems to capture data and totally transform the issues that were discussed earlier this morning.

Somebody said that only less than 1 percent of adverse reactions are reported. If we were capturing a hundred percent of any particular dataset, we would have a totally different perspective on drug safety.

Second, as we move to the computerized prescribing, drug labeling is going to change. Drug labeling right now is a paper-based system. It goes with the dispensing of the drug, or it is put up in a book like the PDR.

Once we are prescribing drugs on our Palm Pilots, what is on the Palm Pilot is going to be what my residents, or interns, or physicians, see.

They are not going to be running around looking for bits of paper anymore. We need to know what is on that Palm Pilot, and we need to ensure that labeling is appropriate to that.

So there are huge opportunities, I think, to transform the way that we do this, and the agency needs the funds, and it needs the intellectual horsepower, and it needs the ability to recruit people who can really do that.

And to do that in a collegial way with all of the stakeholders—industry, academia, and others.

Mr. BILIRAKIS. Doctor, with the indulgence of my colleagues, I let you go because——

Mr. WOOD. Sorry.

Mr. BILIRAKIS. No, it is of great interest to me and to all of us here. I know that Mr. Stupak, in particular, and you might expand in writing on your comments regarding that subject. I appreciate that very much. Mr. Brown.

Mr. BROWN. Thank you, Mr. Chairman. Ms. Pendergast and Dr. Wood, I had—Dr. Wood, you had said as we develop entirely new medicines, particularly those rooted in pharmacogenetics, then regulators in the drug development industries have to think of how efficacy and safety should be demonstrated in entirely new ways.

Most of us have visited biotech firms in our districts or in our regions. I visited a firm called Athersis some time ago, and saw the sort of exciting new things they are doing in research development.

And you see that and you are given the revolution promised by the expediential growth and understanding of how and why disease occurs, and why drugs work in individuals.

Does it make sense, and if both of you would respond, to continue or to separate the regulators into separate entities in this CDER and CBER? Does it make sense to continue that separation, and why?

Ms. PENDERGAST. We are not prepared to make recommendations as the board management changes that the FDA might want to make.

But we do see differences between how biotech products, which are regulated by both the Center for Drugs, and the Center for Biologics, are handled by the number of rounds of review that they take, and the number of months that it takes for the FDA to make a decision.

So what we are proposing in our performance management assessment is that we give the FDA money so that they can do the management, and so they can study what works, and what doesn't work, and so they can develop consistency across the agency.

We are not prepared to tell them what to do, or to manage it. We are just saying please study it. We see major differences. Please, take a look.

Mr. BROWN. Dr. Wood.

Mr. WOOD. I think innovation is going to occur across both those areas, both in CDER and CBER, and I think we need to be prepared to embrace innovation in both areas. And I am not sure that it makes a lot of difference now whether the drug came from a biological background, or came from a chemical background.

Eventually they are going to produce the same novel effects, and some of these effects that we are talking about are going to be in drugs that may have exactly the same action, and exactly the same target, but maybe generated in one case from a biological background, and in the other case from a chemical background.

It makes little sense to regulate these differently, I think, and although there are some issues that obviously are peculiar to biologics that need to be addressed on issues of infection and so on.

Mr. BROWN. Dr. Franson, we all know that prices in the United States for prescription drugs are based in large part on whatever the market will bear, whether you are negotiating with an HMO or whether you are selling to the Federal Government.

And that is not really market will bear, but certainly when you are selling individual drugs to individual consumers. Our neighbor to the north as you know sells its drugs at their pharmacies at much lower prices.

Could you tell me how Eli Lilly, how they sell drugs into the Canadian market, and how those prices are determined?

Mr. FRANSON. Well, that is not an area that I have expertise in, and I am sure that PhRMA or Lilly would be happy to provide you information as you wish in writing.

But as a physician and regulator, I am not even allowed to handle the checkbook at home. So certainly I am not prepared to answer that.

Mr. BROWN. Is that at the office or at home that you are not?

Mr. FRANSON. Both.

Mr. BROWN. All right. That's fine. Thank you, Mr. Chairman.

Mr. BILIRAKIS. Mr. Stupak, you may inquire.

Mr. STUPAK. Well, thanks. Let me pick up where Sherrod left off, Mr. Franson, or Dr. Franson. I realize that you came here to testify on behalf of a trade association and not Eli Lilly, but nonetheless your testimony presents me with an opportunity to clarify just what Eli Lilly and other industry is prepared to do about protecting the safety of patients when the FDA is denied legal tools to compel compliance.

You know, if you take a look at it, post-marketing surveys or risk-management as it is called. First of all, I want to ask you a question that arose last year. The committee was considering the reauthorization of a pediatric exclusivity provision, and at that time the industry opposed it, and did everything that they could to defeat my amendment.

Common sense requirements to require drug companies to make changes in their labels to reflect the results of studies of their drugs in children before they could take an advantage of the 6 months additional exclusivity that you receive for undertaking this

important research, really got their 6 months exclusivity for studying the effects of prozac in children.

You completed the study some time ago. In fact, you received your exclusivity, I believe, last year, somewhere between February and August. So generic was permitted on the market, and so you had a chance to do another 6 months of marketing, which is estimated to be worth $900 million to your executives and your shareholders.

As of January 2002, Lilly still has not changed the label for this drug, while consumers in this country continue to pay for it. What is the status of the labeling change for pediatric exclusivity with Lilly?

Mr. FRANSON. Well, I am happy to answer that, realizing that it has no relationship to PDUFA, but I will tell you that——

Mr. STUPAK. No, no. You will see a pediatric exclusivity fight again in PDUFA, and that's why I am bringing it up, just to refresh your memory. You will see this fight again on pediatric exclusivity.

Mr. FRANSON. I am happy to address that, and I will tell you that I believe that four clinical studies and three clinical pharmacokinetic studies were submitted to the FDA in timely fashion, and those discussions as to labeling remain under review.

So I believe that we have met our obligation and our desire, and we are working with the FDA to expedite that.

Mr. STUPAK. So as of January of this year then, you have submitted your studies?

Mr. FRANSON. We actually submitted it well over a year prior to that.

Mr. STUPAK. A year prior to that? So if there is a labeling change, we still don't know if there is a required labeling change, even though you got your exclusivity last year, right?

Mr. FRANSON. Well, the provision of exclusivity is a submission to data to FDA, with their acknowledgement that it meets their standards.

Mr. STUPAK. But, you know, in your statement, you said that patients should have access to more drugs. But shouldn't patients also have information, access to information? You have the information, Lilly does, and it has been given to the FDA.

You get your 6 month exclusivity, and get $900 million more in profit. All the while, we don't know if prozac, in the dosage and the amount that the doctors have prescribed, is appropriate for adolescents.

And yet you get your exclusivity and your 6 month patent protection. Shouldn't we have that information before you get the patent protection, the extra 6 months? Shouldn't the labeling be done before?

Mr. FRANSON. Well, we certainly acknowledge the importance of providing information to prescribers, and we also recognize our obligations to comply with FDA in terms of labeling, and the pharmaceutical manufacturer, be it my company or others, cannot go out and talk about new uses and so forth, such as in pediatrics, without the approval of FDA, and we respect FDA's oversight.

Mr. STUPAK. But you get the approval before you even have the study completed and submitted, and a label change is even made. That is part of the enforcement problem that we have.

Let's go to PDUFA-2, where you are supposed to do post-marketing surveillance, okay? We here, even though the study has been sitting on the Director's desk for 5 months, we hear that 90 percent of the pharmaceutical companies did not do PDUFA-2 post-marketing surveillance.

Is that a true statement, that 90 percent have not done it under PDUFA-2?

Mr. FRANSON. I actually believe that that is seriously flawed information.

Mr. STUPAK. What is the number then? What is the number?

Mr. FRANSON. Well, I can tell you what our company's number is, because——

Mr. STUPAK. I thought you were on top, on the part of PhRMA, the whole industry, and so I was hoping you would give me that number.

Mr. FRANSON. I do not have an industry number because we have not seen the report from the FDA, but I can tell you that my understanding from colleagues and from the FDA is when their data base was updated, that one is probably looking at 90 percent of studies being completed, and others pending.

So I believe that information was flawed because of poor data submission, tracking and collection by both industry and FDA.

Mr. STUPAK. So that was updated recently then, within the last 5 months, since the study has been sitting on the Director's desk?

Mr. FRANSON. My understanding is that the update that has been submitted would verify that, but I have not seen that, nor have my colleagues. So I think it would be very important to validate that information.

Mr. STUPAK. Well, it is updated on the computer, and we should just go to the computer and we can get the information, and we don't have to wait for the director then do we?

Mr. FRANSON. I'm sorry, but to wait for——

Mr. STUPAK. I mean, if it is all updated on the computer as you said, the computer has been updated, and it is 90 percent completion, and so we shouldn't have to wait for the director.

We should just be able to go to this computer. Do you have the website where we could get this updated information, because I would really like to know about it, because if I am saying something wrong here, I would really like to know about it.

Mr. FRANSON. I think it would be important to see this report which is pending, and we are also anxious to see that. I am certainly glad to verify as a company what kind of commitments have been met.

Mr. STUPAK. Well, you had indicated that it has been updated and it is on a website.

Mr. FRANSON. I did not indicate a website.

Mr. STUPAK. I'm sorry, that the computer was updated, that the FDA updated their computer, I believe you said.

Mr. FRANSON. Our understanding was that that tracking system had not been maintained because it was not a performance goal or requirement.

Mr. STUPAK. But now it is your understanding that it has been updated?

Mr. FRANSON. That is correct.

Mr. STUPAK. And the number is now 90 percent completed and did not?

Mr. FRANSON. My understanding from colleagues with whom I have spoken is that the companies with whom I am interacting have that kind of compliance. We anticipate that would be it broadly, but we have not seen the report.

Mr. STUPAK. Can you tell me what computer has been updated so that I can go there and get the most recent information on this issue?

Because to a lot of us, when you talk about the integrity of PDUFA, there is no integrity when 90 percent of the reports have not been completed. That lessens the integrity of PDUFA.

Mr. FRANSON. I think it would be very important to see that report, and our understanding is that with updates that information is seriously outdated.

Mr. STUPAK. Okay. Well, hopefully we see it before we have any further mark-ups or hearings on this, because it is hard for us on whether or not we should reauthorize PDUFA, especially when we are trying to get to enforcement issues. Do you agree that the FDA should have subpoena power to get to your records, and access to reports?

Mr. FRANSON. I am not aware that the FDA has had any difficulty obtaining any information on inspection, visits, and so forth. So I am not sure what you are asking for.

Mr. STUPAK. Really? Like Serzone, were you here for my opening statement, where with Serzone in 1994, they did a report, and the FDA has been asking for the report, and they still don't have it? That is over 6 years old.

Mr. FRANSON. I am not aware of that situation. I am aware of your reference to it, of course. PDUFA

Mr. STUPAK. Do you believe that they should have subpoena power to get information if it does take 6 years, or in another case, 15 years? Do you think they should have subpoena power to get that information as a regulatory agency concerned with the safety for the American public?

Mr. FRANSON. I think it is important for any regulatory body to be able to validate information that they receive. As to the specifics here, since I have no knowledge, and since it is to a degree a legal matter, I am over my head in that.

Mr. STUPAK. You don't know the difference between subpoena and not?

Mr. FRANSON. What I don't understand is what the gap is, and whether it is a systematic gap.

Mr. STUPAK. Would you support putting the PDUFA-3 agreement in the Federal Register so the public can take a look at it before we authorize PDUFA-3? Would you support that?

Mr. FRANSON. I think it would be very good for all parties to have full knowledge of the kinds of things that have been discussed by those who have directly been involved with PDUFA processes, and probably can offer the best insight on what has worked well, and what can be improved.

Mr. BILIRAKIS. The gentleman's time has expired.

Mr. STUPAK. Thank you, Mr. Chairman.

Mr. BILIRAKIS. Mr. Waxman.

Mr. WAXMAN. Thank you, Mr. Chairman. Dr. Franson, in this recommendation that the industry and the FDA is submitting to Congress to review and to adopt in either form it is submitted to us, or with changes that we might make, we have been told that you pushed forward and got an agreement that requires the FDA to retain an outside consultant whenever an applicant requests one.

This consultant would advise the FDA on an outstanding issue of the applicant's choice during review of a new drug application. Now, it is my understanding right now that the FDA voluntarily retains outside consultants to supply needed expertise.

And, in fact, the FDA did so dozens of times last year in its oncology division alone. It is also my understanding that applicants are always free to bring their own outside experts to meetings with the FDA.

Why do you feel it was necessary to remove FDA's discretion about whether it should hire its own outside expert and place that decision solely in the hands of the applicant; and what was wrong with the voluntary system?

Mr. FRANSON. Well, all I can say is that on PhRMA's behalf, and looking primarily at the Center for Drugs' processes, we are comfortable that the dispute resolution and use of consultants, and so forth, are very appropriate.

And we are comfortable with the FDA's oversight. However, we respect the fact that there are other considerations that are important to address in other centers. And I guess that I would have to defer comment. That is not one that——

Mr. WAXMAN. But am I wrong in assuming that you personally had asked for the mandatory outside consultants to be brought in if an applicant requested it?

Mr. FRANSON. That was not PhRMA's proposal, no.

Mr. WAXMAN. That was not PhRMA's proposal. Ms. Pendergast, was it yours?

Ms. PENDERGAST. Representative Waxman, there is no mandatory requirement that the FDA engage the services of an expert. Rather, the biotech companies have asked that for biotech products only at the Center for Biologics, that a company may ask once the agency to bring in an outside expert into a meeting.

And we will pay for these expert consultancy fees, but the choice of the expert is up to the agency.

Mr. WAXMAN. Why is there a mandatory requirement that the agency must hire an outside consultant?

Ms. PENDERGAST. There is no mandatory requirement. It is totally at the FDA's discretion, and we aren't given additional funds so that they may do this when we ask, but they are under no obligation to do it even when we ask.

Mr. WAXMAN. Thank you. Then that clarifies that issue. Dr. Wood, it appears that even with the money that this agreement will pay toward post-market safety programs, pre-market review will receive far more resources than post-market safety. Do you be-

lieve that post-market surveillance deserves fewer resources than pre-market review?

Mr. WOOD. No. I think it needs adequate resources. I can't tell you that it should be fewer or more, and I would say what I said earlier. I think it is important that we think about drug safety as a continuum.

That there is a continuum that starts with the right studies being done in the early stages before an NDA is filed, and that continues through the relatively small number of subjects or patients who are studied prior to an NDA being filed, and often as few as 2,000 or 3,000 people.

Mr. WAXMAN. Well, back to the adequacy question. Do you feel that that the post-market safety program agreed to under the industry-FDA proposal is adequate to protect consumers from the risk of marketed drugs?

Mr. WOOD. My concern about the rumors, which is what they are, and from what I hear about this agreement, is that there seems to be excessive restrictions on both what these additional FTEs can do, and what they can spend their time doing, although I heard Janet Woodcock say that they won't be people with a star on their hat.

And as specifically designated, there will still be some expectation that at the end of a year that people have spent an appropriate amount of time on PDUFA approved drugs. Drug safety is an overall issue that involves not just the PDUFA drug.

Sometimes it is an interaction with a standard drug. Sometimes the appearances of the toxicity has occurred because of the longstanding, and long approved drug, when in fact it is an interaction with the newly approved drug. So that kind of rigidity seems inappropriate to me.

Mr. WAXMAN. Ms. Pendergast, it is my understanding that at some point in the negotiations between the industry and the FDA, a tentative agreement was reached that would allow user fees to be used to support some drug advertising reviews. Why was that tentative agreement withdrawn?

Ms. PENDERGAST. There was never a tentative agreement. Rather, the FDA has the capacity to, and does use user fee monies, to review advertising, and they are free to do that in the future.

And nothing about this agreement changes either their substantive ability or the standards they impose. The question on the table was if industry gave the FDA more money to review advertising, could the FDA review it quicker.

So the FDA cost it out on how much it would cost to get the FDA to do it faster than it does now, and not better, and not to a different standard, but just faster. And when the FDA came back with how much it would cost to serve the industry by getting their reviews done quicker, the industry looked at it and said of all of the priorities of the things we have to spend money on, this goes to the bottom of the list, or at least below what people were willing to give additional resources for.

So I don't think it is fair to say that in any way, shape, or form, does this stop FDA's review. They are free to devote whatever resources they wish to to it, but it is just speeding it up didn't seem cost effective.

Mr. WAXMAN. Dr. Wood, just on the question of the——

Mr. BILIRAKIS. Just a very brief question and response.

Mr. WAXMAN. The others have had a little bit more time, and I would like just another minute or so. Dr. Wood, do you believe that mandatory use of outside experts is a good policy? If you could answer just yes or no?

Mr. WOOD. I think there are a number of problems with that. First of all—and I will try and be brief.

Mr. WAXMAN. If you could just answer yes or no, and then we can get—because I want to ask just one other question after my time has already expired.

Mr. WOOD. All right. I think it is complex, and I think in an ideal world the answer is no, although there are lots of opportunities. And I personally have served as an expert for the FDA on occasion, and told them to get experts in. I think that is a good thing.

And I think that should be a decision that should be left to the FDA.

Mr. WAXMAN. My last question relates to Mr. Stupak's issue that he raised, and it is my understanding that several of the drugs that were recently withdrawn from the market for safety reasons ran into problems because doctors prescribed them against the label directions, and continued to do so even after the label warnings were repeatedly strengthened.

It looks to me like doctors either don't read label directions and warnings, or don't believe them. Do you believe the FDA should continue to rely on label warnings to solve known safety problems with drugs?

Mr. WOOD. Can I take time to answer that?

Mr. BILIRAKIS. Take time, doctor.

Mr. WOOD. That is a very complicated question, and I think it does merit a longer answer. The issue is that frequently drugs—a problem is identified which people believe can be avoided by increasing the amount of testing that is done on patients prior to them receiving the drug or while they are receiving the drug.

An excellent example is an anti-diabetic drug called Rezulin that caused liver failure, and increasingly frequent liver function tests were ordered, and were suggested in the labeling, to allow Rezulin to remain on the market.

And these were changed every few months, and rezulin was a drug that was being used to treat diabetes. When patients were being asked to return for a liver function test to be performed every 2 weeks, or 3 weeks, that becomes an incredible imposition on a patient's lifestyle, and is clearly unrealistic.

We know that only 7 percent of the patients who were taking Rezulin were actually following these instructions. It may be a problem with physicians, but it clearly is an expectation problem.

It is unreasonable to expect that a patient with a chronic disease like diabetes can come back to the doctor's office on a regular basis to have liver function tests drawn when they have another life. They have got a job and so on.

So we need to work out how we are going to manage these risks better, and this is a complex question, and it involves education of physicians, and it involves setting reasonable expectations.

It involves defining and making certain that introducing these restrictions actually improves safety. That is not always the case. And sometimes there is just a desire to do more.

And so I think it is a very complicated question, and I think the answer is unclear, and I think it is something that we need a lot more work on.

Mr. WAXMAN. Thank you, Mr. Chairman.

Mr. BILIRAKIS. All right. Mr. Green, do you have questions of this panel?

Mr. GREEN. I will try and be brief, Mr. Chairman. I appreciate it. I'm sorry I was not here earlier for the first round, but it is the nature of the business. If any of the panel could—one of the criticisms of PDUFA has been that some of the drugs that are receiving priority are neither innovative nor life-saving.

While we all appreciate the need for drugs to treat, for example, male pattern baldness, we certainly want to make sure that truly innovative drugs are receiving the highest priority at the FDA.

And we understand that the FDA has a process whereby certain NDAs receive priority in the review process. Can any of you share some information about that concern that maybe some of these pharmaseuticals are not necessarily life-saving or innovative?

Mr. WOOD. Well, male-pattern baldness sounds like a pretty high priority for me.

Mr. GREEN. Well, I have to admit that I may be getting there, but it is not life-saving.

Mr. WOOD. I think if I could respond to that. I think one of the things that we do at our peril is apply paternalistic views to patients' suffering, and sometimes—and I plead guilty to that, too.

And the drugs that have been used for diseases that patients truly suffer from, but may not be life-threatening, can still be very debilitating for patients. Novel therapies for these diseases still should receive rapid review and approval, because they can still be very debilitating for patients.

I am only being a little facetious about male-pattern baldness, but irritable bowel syndrome, for instance, which doesn't sound such a serious disease to some patients, has devastating effects in one's life.

It is clearly not life-threatening, but devastating effects in one's life. So I think we need to be—and we meaning experts, need to be careful about adopting an attitude that views life-threatening as the only criteria for urgent approval.

Mr. GREEN. And again it is a priority, I guess.

Mr. WOOD. Right.

Mr. FRANSON. And I was just going to add that the category of priority reviews are usually made on the basis of an unmet medical need, which can include, but isn't limited to, life-threatening illness.

And the determination on that is not made by the sponsor submitting the application, but by the FDA.

Mr. GREEN. Mr. Chairman, just one more question. Ms. Pendergast, in your testimony you presented about BIO, it makes clear that your organization is concerned about both CDER and CBER meet the review times set out in the performance goals.

The CBER takes longer and more cycles to approve biologic based drugs; is that correct?

Ms. PENDERGAST. Yes, sir, it is. If we look at the data for the last 4 years of PDUFA-2, what we see is that year in and year out the Center for Drugs is able to organize itself such that roughly half of all drugs are finally reviewed on the first cycle.

Whereas, that percentage for the Center for Biologics is only 20 percent. The differences are also striking in terms of the number of months it takes for the FDA's consideration for them.

Again, the Center for Drugs is simply faster than the Center for Biologics, and we would like to understand the reasons for those differences.

Mr. GREEN. I think some of us would also to see if there is an interest in it. We are informed that the FDA also enacted with PDUFA-2 when it was reauthorized provides for something called special protocol reviews, whereby firms presumably through the advantage of inexperienced companies that more typically submit their applications, the CBER can take advantage of the FDA expert assistance in designing that special protocol that binds the FDA, absent scientific breakthrough to accepting the terms of that protocol in the review process. Is that correct?

Ms. PENDERGAST. Yes, there are certainly many more companies that have availed themselves of this opportunity for consultation with the agency, and the Center for Drugs than for the Center for Biologics.

Again, we are not giving the reasons for this widely disparate set of numbers, but we are offering to give the agency additional resources so they can conduct studies to find out why it is that companies are so hesitant to do it, and why the FDA is so hesitant to offer this service for biotech companies.

Mr. GREEN. How many members of BIO are also members of PhRMA or not members? Is there——

Ms. PENDERGAST. The vast majority of the members of BIO are not also members of the Pharmaceutical Manufacturers Association. There are a few, and we would have to get that for the record, but it is probably less than 10 percent.

Mr. GREEN. Okay. Do you believe that Dr. Zoon puts less pressure on her reviewers than Dr. Woodcock, or do you want to touch base on that?

Mr. BILIRAKIS. Are you going to withdraw that?

Mr. GREEN. I will withdraw it. Thank you, Mr. Chairman.

Mr. BILIRAKIS. Mr. Bryant to inquire.

Mr. BRYANT. Thank you, Mr. Chairman. Dr. Wood, I have rushed back here so that I could be sure to let you see me here so that you could go back home to Tennessee and tell people I am working.

Mr. WOOD. I will be sure to tell them that.

Mr. BRYANT. We don't work away from these rooms here. Let me ask you, and I know that I am sort of catching up here, and you have already given your testimony and answered a number of questions, but the performance goals which accompany the PDUFA focus on review times, I know that you are very interested in finding ways to shorten the clinical developmental time or development times.

Do you have any suggestions on how to best shorten clinical development times?

Mr. WOOD. Yes. I think we need to avoid doing studies that are either of low quality—and I don't mean that they were not performed right, but were done because somebody perceives the FDA may ask for them later.

And we need an increased certainty that a package of studies put together will indeed satisfy the agency when they get there, and that was addressed a moment ago. And so I think we need to work as a group with all the stakeholders to work out what it is that we are going to need to do to get a drug approved.

In many examples that are currently out there, we don't know that right now. We are talking about novel therapies that work by novel approaches, and that work in ways that have not been seen before.

And we are going to have to put a lot of effort, and the agency is going to have to spend a lot of time and effort in working out what the best approach to these new drugs is. And that is going to have to be done in a way that reassures industry that if they follow that approach that they will target approval if the studies come out the right way obviously.

Mr. BRYANT. In your written testimony, and I believe in your oral statement today also, you speak about the need to find new ways to measure efficacy. In the future should this debate be a part of the PDUFA negotiations or should it be left solely to the agency?

Mr. WOOD. The reason that I emphasized that is that I think it is important that the agency have sufficient funds independently of PDUFA, and to allow them to make the innovative changes that we are going to have to do.

That is going to take a lot of time, and it is going to take a lot of consultations, and it is going to take a lot of effort. And this should not become a distraction in NDA approvals, but it will take effort, and that seems to be an appropriate reason for funding to be increased.

The past is not going to be a prologue to the future here. We are going to have to make paradigm shifts in the way that we think about drugs, and that is going to take effort and expenditure.

Mr. BRYANT. You speak of pharmacogenetics, and I am not pronouncing that correctly. Do you believe that we will ever get to the point where drugs and biologics are only approved for certain individuals with specific genetic makeups?

Mr. WOOD. Well, that is a very interesting question,and one that the FDA and industry really need to work on, because what we don't want—we want to encourage the development of drugs for identified patient populations.

We want to discourage patients who are not going to respond to drugs getting drugs, and we want to discourage patients who are going to develop adverse effects getting these drugs.

And industry on the other hand, and I shouldn't speak for them, I guess, but industry is also worried that they don't get an overly restrictive label for a drug, and that would restrict the potential market for the drug.

So somehow we need to work to use the genuine benefits of pharmacogenetics to allow us to better target drugs to our patients without limiting the potential for these drugs in the future.

Mr. BRYANT. Do either of the other witnesses on the panel have brief comments on any of those questions, or would like to add to, or take away from?

Mr. FRANSON. I would just say that the notion of pharmacogenetics, and the opportunity that it does offer is exciting and probably will be a centerpiece for PDUFA-4, given the time that it will take to evolve.

And I would just say that we would foresee the same high standards of efficacy and safety being held in approval, but perhaps different measures to get at those end points.

Ms. PENDERGAST. I would just like to say that while today we are talking about the funding that the companies are providing to the agency, I would like to underscore what Dr. Wood said before.

In an era where we are doubling the NIH's budget, we know that the products that they are studying and developing will come to the FDA 5 years down the road. And there will be paradigm shifts in terms of the impact of the genetic revolution, pharmacogenomics.

And I urge the Congress to consider increasing the appropriations for FDA and not rely obviously just on what bit the companies can throw into the pot.

Mr. BRYANT. Thank you, Mr. Chairman.

Mr. BILIRAKIS. Thank you, Mr. Bryant.

Mr. BROWN. Mr. Chairman, I want to make sure that—and again I think you had already done this, but any members that have written questions for the panelist—Dr. Franson—I had asked him about the Canadian pricing, and if you or the people at PhRMA would answer that.

Mr. BILIRAKIS. Yes. Members have 3 days to submit questions to the committee and we will submit them to you. I know that you would be very pleased to respond to them.

Obviously your response being sooner rather than later would be very helpful. The knowledge that you all have is just terrific, stupendous, and it is going to be of great benefit to us.

Again, I not only ask you to respond to the questions, but submit to us any information voluntarily that might help us do our job. Thank you very much. The hearing is adjourned.

[Whereupon, at 1:42 p.m., the subcommittee was adjourned.]

[Additional material submitted for the record follows:]

RESPONSES OF THE FOOD AND DRUG ADMINISTRATION FOR THE RECORD

QUESTIONS SUBMITTED BY CHAIRMAN MICHAEL BILIRAKIS

1. Is the United States now the country where most new drugs are first-approved? Was this the case prior to PDUFA?

Yes, the United States (U.S.) is now the country where most new drugs are first approved. A study by the Tufts University Center for the Study of Drug Development confirmed that FDA's implementation of PDUFA has helped enable American patients to be first in the world to have access to many new drugs. During the years 1991-1995, drugs were first marketed in the U.S. only 31 percent of the time. During the same period, drugs marketed for the first time in other countries were first marketed in the U.S. within a year of their foreign introduction only 43 percent of the time.

During the period 1996-1998, however, nearly 47 percent of all new drugs marketed world-wide were first marketed in the U.S., and American patients had access

to 78 percent of the world's new drugs within the first year of their introduction. (Kaitin, KI. "Impact of the Prescription Drug User Fee Act of 1992 on the Speed of New Drug Development." Tufts University Center for the Study of Drug Development, prepared for FDA Public Hearing on PDUFA, September 2000.)

2. I understand that after this year there will be no carry-over funds available to pay FDA reviewers. That is, if the Congress doesn't reauthorize the program, FDA will have to lay-off employees. Is this the case? If so, how many reviewers will have to be laid off? When will these employees first be notified of the possibility that they may be laid-off if the program is not reauthorized?

Your understanding is correct, Mr. Chairman. FDA will have virtually no carry-over PDUFA funds available to pay our employees when the fiscal year ends on September 30, 2002. FDA currently has about 2,400 staff-years devoted to the drug review process. Since prescription drug user fees are used to support approximately 50 percent of the staff devoted to the drug review process, FDA will begin planning for a furlough and/or a reduction in force (RIF) in June and by August 1, 2002, we would issue a general notice of a possible RIF to all 2,400 employees.

3. FDA has stated that increasing revenues and addressing risk management were its top two priorities in the discussions with industry. How successful was FDA in addressing these issues in the negotiations?

FDA believes that both of these priorities are successfully addressed in the proposed Goals Letter and proposed statutory changes to PDUFA. If these recommendations are enacted into law, FDA will receive a substantial increase in funding. Fee revenues would increase from an estimated $148 million in Fiscal Year (FY) 2002 to $222.9 million in FY 2003. Ultimately, fee revenues would increase to $259.3 million in FY 2007. The increased fee revenues would enable FDA to achieve both the letter and spirit of the performance goals. Increased resources would be available for increased staffing, training, guidance development, and other key aspects of the process for the review of human drugs.

The proposed funding for risk management activities would allow FDA to double its safety staff by FY 2007. The increase in staff and resources would enhance FDA's ability to monitor new drugs for safety problems that could emerge after their introduction on the U.S. market. Enhancing this programmatic ability is especially critical now that U.S. patients are increasingly the first population to receive new drugs.

4. You state in your testimony that PDUFA performance goals have helped harmonize drug and biologic product review. However, on January 25, 2002 FDA issued a report on review times, and it shows that CDER reviews and approves priority drugs in six months, but that CBER reviews priority biologics in 11.5 months and approved them in 13.2 months. Similar disparities existed for standard reviews. Why the disparity between the two Centers?

The Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) have met the performance goal deadlines for review and action on priority (90 percent within 6 months) and standard (90 percent within 12 months) applications. Approval times, on the other hand, have differed between the Centers. Although there has been no systematic study of the reasons for these differences, the Agency believes that they are the result of multiple forces including the difficulties that applicants experience in manufacturing the product. Another problem that occurs frequently with biological products is the inability to "scale-up" the manufacturing process. The sponsor can produce a batch of product for clinical trials, but when larger scale production is initiated the product no longer meets the same specifications as the product tested in trials. These difficulties can lead to longer approval times.

5. What will be done under PDUFA III to lessen the disparity in review and approval times between CDER and CBER?

The PDUFA III proposals recommended to Congress include several initiatives to evaluate and address differences between Centers. The First Cycle Review Performance initiative provides for increased communication (e.g., of the early-identified deficiencies) to the sponsor at the time of the filing review and the development of a guidance document by review staff on Good Review Management Principles. This initiative includes further training to implement those principles, and a study to evaluate best practices on the part of both FDA and industry during the first cycle of review. The Performance Management initiative includes funding for a review and analysis of the review process in both Centers.

6. I understand that one key component of the tentative agreement made between FDA and industry relates to performance management. Specifically, FDA has agreed to a study of internal management and performance.

Please describe for us the nature of the performance management agreement and how your office will ensure that this important piece of PDUFA III is fulfilled.

FDA's Office of the Commissioner will conduct a series of studies to identify opportunities for enhanced program performance. These will include a study through an outside consultant to perform a comprehensive process review within CDER and CBER. The anticipated outcome of this review will be a thorough documentation of the drug and biological review process, a re-map of the process indicating where efficiencies can be gained, activity-based project accounting, optimal use of review tools, and a suggested path for implementing the recommendations. FDA would anticipate delivery of a report of the consultant's findings and recommendations in FY 2004-2005. The Agency would consider these recommendations in planning any redesign or process reengineering to enhance performance.

7. Recent data indicate that drug approval times have been increasing. The approval times for novel drugs ("NCEs") have increased from 12.6 months to 17.6 months between 1999 and 2000. What are the reasons for the upward trend?

The median total approval time for priority new molecular entities (NMEs, i.e., drugs not previously approved by FDA) approved by CDER has been approximately 6 months for the past 5 calendar years (1997-2001). Over the same 5 calendar years, the median approval times for standard NMEs approved by CDER have ranged from a low of 13.4 months in calendar year 1998 to a high of 19.9 months in calendar year (CY) 2000. For calendar year 2001 the median approval time for standard NMEs was 19.0 months.

While FDA has met or exceeded all of its performance goals for the review of NME applications during PDUFA II, the median total approval times for NMEs over the past three calendar years have been higher compared to the all-time low of 13.4 months experienced in CY 1998 (16.3 months in CY1999, 19.9 months in CY2000, 19.0 months in CY2001). There are many factors that may affect the total approval times for standard NMEs in any calendar year including the quality and completeness of the applications and the time required for the sponsor to resolve any safety, efficacy, or manufacturing deficiencies identified by FDA. However, FDA has noted that the trend of increased total approval times for NMEs during the past three calendar years has coincided with implementation of the increased procedural goals (e.g., meeting management goals) under PDFUA II. FDA believes that the increased workload it has experienced during PDUFA II and the implementation of FDAMA requirements may have contributed to this trend. It is important to note that a similar trend has not been seen for priority applications or for standard non-NME new drug applications (NDAs).

8. When will the FDA issue its draft guidance on use of surrogate markers in imaging?

The only guidance that FDA is developing on medical imaging is the guidance for industry on Developing Medical Imaging Drugs and Biological Products. This guidance for industry is being developed with extensive input from the public. A first draft of the guidance was issued for comment on October 14, 1998. FDA held public meetings on the draft guidance on January 25 and March 26, 1999. After considering the discussion and comments at the meetings and after reviewing all written comments, FDA issued a second draft for comment on July 31, 2000. The Agency has considered carefully the second round of comments, and the final version of the guidance is currently moving through the clearance process. We expect it to be released during the next month or two.

9. When will FDA address the cGMP requirements for PET products?

The Food and Drug Administration Modernization Act (FDAMA) directs FDA to consult with patient advocacy groups, professional associations, manufacturers, and physicians and scientists who make or use PET drugs as we develop PET drug CGMP requirements and approval procedures. We have taken extraordinary steps to develop the PET CGMPs with extensive input from these groups. We presented our initial tentative approach to PET drug CGMP requirements and responded to numerous questions and comments about that approach at a public meeting on February 19, 1999. In the September 21, 1999, issue of the Federal Register (64 FR 51274), we published a notice of availability of preliminary draft regulations on PET drug CGMP requirements. These preliminary draft regulations were discussed at a public meeting on September 28, 1999. After considering the comments on the preliminary draft regulations, FDA has decided to make several changes to those regulations, to publish a notice of availability of a revised preliminary draft proposed rule, and to publish an accompanying draft guidance document. These documents should publish very soon. We intend to hold another public meeting on May 21,

2002, after which we will evaluate the comments, make appropriate changes, and publish a proposed rule for comment.

10. To what extent has CDER and CDRH worked to harmonize requirements for drug and device manufacturers seeking similar indications (e.g., perfusion indications for MR/US drugs and MR/US machines)?

CDER, the Center for Devices and Radiological Health (CDRH) and the FDA Ombudsman's office work together to assure that sponsors of similar drug/device products are treated the same with respect to regulatory requirements and review procedures. If any company believes they are being treated differently than similarly situated competitors, they are encouraged to bring the issues to the FDA Ombudsman or to the CDER or CDRH Ombudsmen.

QUESTIONS SUBMITTED BY REPRESENTATIVE JOHN D. DINGELL

What is the legal status of the side agreement? Specifically, is this a contract, a regulation, a guidance, or something else?

The document referred to as the "side agreement," which is a letter sent from the Secretary of the Department of Health and Human Services (HHS) to the Committee on Energy and Commerce of the House of Representatives and the Committee on Health, Education, Labor, and Pension of the Senate (the "Goals Letter"), is not a contract, regulation, or guidance. The goals letter is a statement by the Secretary about what the FDA intends and expects to accomplish with the additional resources provided through the proposed legislation. This letter is specifically referenced in the proposed PDUFA legislation in the findings section (section 101) and in the section specifying annual reports (section 104).

Does this side agreement create any enforceable rights on the part of industry or FDA? If so, please describe these.

The Goals Letter does not create enforceable rights on the part of industry or FDA. The PDUFA III legislation, if enacted, would provide FDA the authority to collect and spend user fees as specified in the enacted legislation.

Are the provisions of the side agreement enforceable in any way by third parties?

No. However, there is substantial oversight of FDA's activities under PDUFA that allows the Administration, Congress, the regulated industry, and all other interested persons to evaluate FDA's performance on a regular basis. The proposed PDUFA legislation, if enacted, would direct the FDA to provide both an annual performance report and an annual financial report setting forth its performance in achieving the goals and its expenditures from PDUFA funds, as it has during PDUFA I and II. Both of these reports are made available to the public.

If enforceable by anyone, what are the available remedies?

As discussed above, while neither industry nor other interested persons can file suit against FDA to enforce the performance goals contained in the letter, the annual reports provide Congress, regulated industry, and other interested persons with the information about the Agency's accomplishments and use of funds collected under the PDUFA.

Is FDA free to modify or ignore any or all of the provisions of the side agreement for any reason? Can it modify or ignore the agreement in the name of public safety?

FDA fully intends and expects to perform in a manner consistent with the Goals Letter. FDA's performance under PDUFA over the past 10 years demonstrates that this expectation is likely to be met. Under the PDUFA legislation, FDA may only use user fees for health activities related to the process for the review of human drug applications. If a public safety emergency required FDA to shift resources away from the process for the review of human drug applications, FDA could shift resources, but would not be able to collect or spend user fees for any activities not authorized by PDUFA.

On page eight of your testimony you compare product withdrawals pre PDUFA and during PDUFA and conclude that drug safety has not suffered because withdrawal rates are basically the same. Can you comment on drug safety issues that are of concern to FDA, but that do not result in product withdrawals? For example, could you provide us with a pre PDUFA and PDUFA comparison of such post market drug safety matters as warning letter, package inserts, black boxes and the like taken by FDA other that withdrawals?

A report to the Commissioner of FDA from the Task Force on Risk Management entitled, "Managing the Risks from Medical Product Use" was issued in May 1999. This report is enclosed as Appendix 1. Appendix A of the enclosed report provides

a comparison of post-approval risks for drugs and biological products approved before and after the implementation of PDUFA.

Could you outline in detail each element of the side agreement? I realize that it is still undergoing departmental review, but it would be helpful to us to have a run down of the agreement now. Will you provide us with written text of the agreement as it currently stands?

Since the Subcommittee held its hearing on March 6, the Administration has transmitted the Goals Letter to the Energy and Commerce Committee. The full text of the Goals Letter appears in Appendix 2.

Can you explain for us exactly why this side agreement needs to be cleared by OMB. That sounds a lot like a regulation. If so, why aren't APA notice and comment procedures being followed?

Regulations are not the only documents appropriate for the Office of Management and Budget (OMB) clearance or review. OMB reviews budget estimates as well as documents in support of pending or planned legislative proposals. (See OMB Circular A-19 for the policy on clearance of legislative proposals and Circular A-11 for the policy on clearance of budget matters). The Goals Letter is, in part, a budgetary matter since it involves Agency resource commitments. It is also referred to in a legislative proposal that the Administration has decided to advance for FY 2003. For these reasons it is appropriate for OMB review. Because the Goals Letter is not a regulation, the Administrative Procedure Act (APA) requirements for notice and comment rulemaking are not applicable.

Could you explain the pros and cons of subjecting the side agreement to notice and comment in the Federal Register before making it final? Wouldn't such a procedure provide a broader base of input to FDA and a greater assurance to all that the agreement is in the public interest?

FDA believes that this process, as well as the legislative process that Congress engages in, provides great assurance that the PDUFA program will continue to be in the public interest. In order to receive input from a broad range of interested persons on the concepts in the proposed legislation and Goals Letter, FDA hosted a series of discussions over the past 18 months. Since the fall of 2000, FDA has engaged in a series of public meetings with patients, consumers and other stakeholders to obtain their views on their issues and priorities for PDUFA reauthorization. FDA has also engaged in a series of meetings with representatives of the biotechnology and pharmaceutical industry to discuss some of the more technical aspects of application review, information technology in support of application review, and fee collection and use.

RESPONSES TO THE RECOMMENDATIONS AND/OR CONCERNS RAISED IN THE PAPER COMPILED BY THE PATIENT AND CONSUMER COALITION, AS REQUESTED BY REPRESENTATIVE JOHN DINGELL.

Hold balanced hearings on PDUFA reauthorization and drug safety concerns. The hearings should include testimony from patients who have been harmed by problem drugs—or their representatives—and consumer advocates who are knowledgeable about PDUFA. Such hearings would send a vital signal to FDA from Congress that what the public wants and deserves is a thorough review and oversight process for drugs and biologics, not just speedy approval of new products.

FDA defers to the prerogatives of the Energy and Commerce Committee to determine the choice of witnesses for its hearings.

Adequately fund the entire range of FDA's approval and safety oversight activities from general revenues. There is an urgent need for increased funding for post-marketing surveillance and other safety-related activities not covered by current user fees. User fees are not a substitute for adequate federal funding of these vital and growing public health functions. Adherence to this principle would be the surest way to remove the worrisome potential for conflict-of-interest that arises when dedicated income streams flow tot he regulator from the regulated industry.

Administrations, both past and present, as well as Congress have determined that the process for the review of human drugs and biologics at FDA should be funded through a combination of appropriations and user fees. FDA has been able to administer this policy without compromising its integrity or the safety and efficacy of the products it approves.

Give the FDA Total Control Over All Review and Surveillance Activities—If an unwillingness to appropriate adequate funds leads Congress to consider the expansion of user fees, it is absolutely essential that the FDA alone determine their usage, without the kind of inappropriate control

over the use of these fees (through mandated decision-making deadlines) that the industry has exercised with new drug approvals.

Under PDUFA, fee revenues may be used by FDA to cover the costs of the process for the review of human drugs. In the context of receiving these additional revenues, FDA agreed to meet certain performance goals for the review of applications and certain procedural and processing goals. FDA retains the ability to allocate the fee revenues as it sees fit in order to meet its public health obligations and to meet the PDUFA performance goals. It is important to remember that the performance goals in PDUFA relate to the timeliness of review and processing of applications, not the approval of applications. FDA believes that the current system works well and the PDUFA program has overall been good for the public health.

Address Drug Safety Concerns Created by PDUFA's Excessive and Inappropriate Focus on Swift Approval—PDUFA III should include new safety protections that, to the greatest extent possible, protect the public from potential harm caused by adverse reactions, side effects and adverse events related to pharmaceutical products and biologics. Decision-making deadlines for drug review should be redefined to focus on the FDA's responsibility to guarantee safe drugs, not only on the speed with which reviews are conducted. The agency's antiquated and under-funded adverse event reporting system (for drugs, biologics and devices) should also be modernized.

A report to the Commissioner of FDA from the Task Force on Risk Management, entitled, "Managing the Risks from Medical Product Use" was issued in May 1999. That report (enclosed as Appendix 1) found that, for drugs approved during the PDFUA era, the rate of drug withdrawals for safety concerns was relatively unchanged from the rate of drug withdrawals for safety concerns in the pre-PDFUA era. The most recent data show that the percentage of PDUFA drugs withdrawn for safety concerns is the same (2.7%) as the percentage of drugs withdrawn for safety concerns during the pre-PDFUA period (2.7%). This finding is particularly notable when one takes into account the fact that nearly 80% of newly approved drugs are either approved first in the United States or are approved in the United States within one year of their being approved anywhere else in the world.

The draft Goals Letter for PDUFA III includes no substantive changes to the performance goals for review of applications compared to those currently in place. The draft Goals Letter also includes a proposal for an expanded risk management program for new drugs approved under PDFUA III. FDA believes that this new risk management program will significantly enhance its ability to detect risks of drugs early and improve FDA's ability to work with the sponsor, health care providers, and patients to manage the risks of new drugs more effectively. The proposal for PDUFA III would allow FDA to use PDUFA fee revenues to cover the costs of this new risk management program, including activities that occur for up to three years after drug approval. The availability of these new PDFUA fee revenues for risk management would allow FDA to approximately double the staffing in its drug safety program over five years.

Please refer to the response provided to the question below relating to "Improve Adverse Event Reporting" for details relating to adverse events.

Eliminate the linkage between appropriated and user fee funds. The current law results in disproportionate funding for the drug approval process compared to most other research, regulatory, and public education functions. At a minimum, the program must be re-designed in such a way as to prevent the draining of funds from vital FDA functions.

During the period of FY 1994 to FY 2001, the effect of the statutory triggers established under Prescription Drug User Fee Act (PDUFA) on the availability of funding for non-PDUFA programs has been less significant than the absence of additional appropriations to fund the annual pay raises for Food and Drug Administration (FDA) employees. During these years, FDA's appropriations failed to include increases to cover the annual costs of mandated Federal pay raises. The cumulative impact of absorbing the cost of the Federal pay raise during this eight-year period was more than $200 million. This resulted in a reduction in staffing for activities other than the process for the review of human drug applications (e.g., compliance activities, review of over-the-counter drugs, etc.) of more than 1,100 staff years since PDUFA I was enacted.

Although the absence of additional funds to pay the cost of mandated pay raises has had the greatest effect on non-PDUFA programs, one of the PDUFA triggers has also had a significant effect. Section 736(g)(2)(B) requires that FDA annual spending on drug review from appropriations be at least as much as the amount of appropriations that FDA spent on drug review in FY 1997, adjusted for inflation.

The legislation that the Administration has proposed includes modifications to the trigger (Section 736(g)(2)(B)) such that FDA will no longer be compelled to spend amounts that are significantly greater than the amount required by this trigger. The proposal would provide FDA a margin of error in its effort to meet this requirement of the law. Under this proposed modification, if FDA's spending from appropriations on drug review is within 5 percent of the amount required by this section of the law, the requirement is considered to be satisfied. In cases where FDA's spending from appropriations is within 3 percent of the trigger amount, no adjustment in fees will be required. If the spending is between 3 percent and 5 percent below the trigger amount, then FDA will, in a subsequent year, decrease user fees by the amount of the shortfall that is between 3 and 5 percent (i.e., a maximum of 2 percent).

The purpose of this change is to relieve FDA of the need to overspend from appropriations each year, as has occurred consistently since FY 1993. Spending from appropriations on the drug review process each year is still expected to be at, or very close to, the amount specified by this trigger, and may never be more than 5 percent below the trigger amount.

Require that user fees support the life cycle of the review process. Presently, FDA staff hold numerous pre-New Drug Application meetings with manufacturers before the agency receives any PDUFA fees for the intended application. While these meetings benefit sponsors greatly by improving their understanding of FDA expectations and the quality of their applications, they also divert FDA staff time from other review functions and increase the cost and difficulty of meeting PDUFA goals. In other words, the required meetings are an un-funded mandate on the agency.

The financial provisions in the legislation that the Administration has submitted should satisfy the concerns that prompt this issue.

First, it is important to note that PDUFA revenues come from three fees—application fees, product fees, and establishment fees. The fees from all of these sources can be used by FDA to enhance its activities in any part of the drug review process, from the submission of an investigational new drug application through the FDA decision to approve or not approve a new drug application. Some of the revenue from product and establishment fees is used to support the work FDA does at the investigational new drug stage, before a marketing application is ever submitted.

The Agency agrees that under PDUFA II, FY 1998 through FY 2002, fee revenues were insufficient to adequately fund the work necessary to meet the PDUFA II performance goals. The legislative proposal that the Administration has forwarded to the Energy and Commerce Committee addresses this problem by significantly increasing the revenue levels from FY 2003 through FY 2007. This proposal calls for revenues of $222.9 million in FY 2003—a 30% increase over revenue levels FDA expects to spend in FY 2002. These revenue levels will rise to $259.3 million by FY 2006 and 2007—an increase of more than 50% compared to FY 2002 spending levels. Further, these figures are in FY 2003 dollars, and will be adjusted to account for the impact of inflation and workload increases. FDA believes that this proposal would fully fund the work obligations that would be required of the Agency over the next 5 years.

Finally, under the proposal, FDA would be allowed to use fee revenues to fund some activities that the Agency will perform after a drug is approved. For drugs approved on or after October 1, 2002, risk management and epidemiological studies that may be needed in the first two to three years after approval may be paid for from PDUFA fees. The Agency expects that this provision will enable FDA to approximately double its headquarters drug safety employment levels in CDER and CBER by FY 2007. We believe that this is an important addition to the resources available to FDA that helps to assure the safety of drugs in their first two or three years of market life.

Question Consult All Stakeholders—If performance goals are not eliminated in PDUFA III, consumers and patient representatives should be involved in developing them.

FDA has conducted a fair and balanced effort to hear from all parties that have a viewpoint about PDUFA. In preparation for submitting the Administration's PDUFA III proposal to Congress, the Agency engaged in a comprehensive initiative to involve all PDUFA stakeholders—consumers, health providers, patient groups, and the manufacturers of drugs and biologics—in the development of PDUFA III proposals. This process included:

- Two public hearings.
- "Listening" sessions with consumer and patient groups.
- Consumer roundtables where PDUFA was a major topic of discussion.
- Meetings with drug and biologic manufacturers.

At our public hearings, FDA received 12 hours of testimony. Of the total of 28 witnesses who provided testimony, 23 were representatives from consumer, patient and health provider groups. Seventy-five consumer, patient and health provider groups were also represented at the "listening" sessions and roundtables. This is evidence of the broad representation that served as a foundation for the Administration's PDUFA III proposal and the development of the PDUFA III performance goals.

Grant FDA a "Scientific Override"—When the FDA requires additional information or clarification from the manufacturer as part of the review process, the FDA should be allowed to "stop the clock" on review deadlines while waiting for this information to be provided.

The fundamental premise of the performance goals for review of applications outlined in the letter from the Secretary of HHS to Congress is that sponsors are expected to submit a complete application for FDA review and FDA will perform a complete review of the application within a defined time (i.e., 6 months for priority applications and 10 months for standard applications). If FDA determines during the review of an application that additional information is needed from the sponsor, FDA may request the information from the sponsor while continuing its review of the application as submitted. If the additional information is submitted to FDA during the same review cycle, FDA has several options on how to handle the new information. If there is sufficient time remaining on the review clock, FDA may choose to review the new information without changing the review clock. Alternatively, FDA may choose to extend the review clock by up to three months if the new information constitutes a major amendment to the application and is submitted within the last three months of the review cycle. Finally, FDA may defer review of the new information until the next review cycle. Thus, FDA already has a significant degree of discretion in deciding how to process new information submitted during the review of an application and FDA considers these options sufficient to address issues that arise when new information is submitted to an application during a review.

Eliminate Rigid Management Goals—These goals require the agency to set up meetings with the industry within specific timeframes. They should be replaced by a more flexible system that allows the FDA to prioritize these requests, thus decreasing undue burden on the agency.

FDA is satisfied with the current prioritization of meetings into three categories, such that a meeting about a critical issue takes precedence over a more routine discussion. Type A meetings are considered necessary for an otherwise stalled drug development program to proceed (a "critical path" meeting). For example, a Type A meeting would be held when FDA has placed an investigational new drug on "clinical hold" and the investigation cannot continue. Type A meetings are held within 30 days. Type B meetings are usually held to discuss anticipated submissions (pre-initial IND, end of Phase II, or pre-NDA) and are held within 60 days. Type C meetings are any other type of meeting and accordingly, have the longest timeframe of 75 days. Fee revenues in the proposed statutory changes for PDUFA provided the necessary resources to support these meetings.

Allow FDA More Flexibility For Standard Reviews—There is no public health justification for requiring the FDA to decide on a "me too" drug that duplicates therapies already on the market at the same speed as a drug that might offer therapeutic advantages to some patients. The FDA should be granted greater authority to prioritize the review of standard drug applications.

FDA has existing criteria by which decisions are made regarding whether to prioritize the review of new drug applications based on the therapeutic potential of the drug. The two review classifications and their definitions are:

- Priority review drug—The drug product, if approved, would be a significant improvement compared to marketed products in the treatment, diagnosis, or prevention of a disease. Improvement can be demonstrated by, for example: (1) evidence of increased effectiveness in treatment, prevention, or diagnosis of disease; (2) elimination or substantial reduction of a treatment-limiting drug reaction; (3) documented enhancement of patient compliance; or (4) evidence of safety and effectiveness of a new subpopulation.
- Standard review drug—All non-priority applications will be considered standard applications.

Under PDUFA, the review clock for priority applications is 6 months and the review clock for standard applications is 10 months. FDA's performance goals for a complete review of both types of applications are 90% completed within the goal dates.

FDA believes that the current system for designation of products for priority review and the current review clocks and performance goals work well and allow FDA

to prioritize its review work. The PDUFA III proposal would not change the current performance goals.

Create Safety Goals—FDA should establish performance goals oriented toward protecting the health and welfare of consumers, such as tracking and reviewing Phase IV trials, improving the collection, analysis and response of adverse event reports, and enhancing the speed and quality of review of direct-to-consumer advertisements.

The PDUFA III proposal does not include performance goals for the activities identified in this question. However, FDA has conducted, and will continue to conduct, significant activities in the areas identified in this question. Details of these activities follow:

Tracking and Reviewing Phase IV Trials

Following the enactment of FDAMA, FDA initiated a number of steps to implement the provisions on postmarketing studies (section 130). In addition, several procedural improvements were made and a data tracking system was developed to improve monitoring and processing of annual status reports and final study reports. The improvements include:

- Updating staff operating procedures at CDER to clarify how postmarketing commitments and the annual status reports will be processed, reviewed, and archived.
- Designating CDER personnel to be responsible for monitoring the submission of reports. Target review timelines have been established for annual status reports and for the review of final study reports. These timelines will be tracked and monitored.
- Developing new CDER data systems to more efficiently capture the existence of postmarketing commitments, the submission of annual study progress reports, the submission of final study reports, and final review determinations. This new database was implemented in July, 2001.

Improving the Collection, Analysis and Response of Adverse Event Reports

One of the objectives of the risk management component of the PDUFA III proposal is to develop surveillance approaches in a directed and well thought out manner that could yield the greatest value for the particular drug. In circumstances where there are suggestions in the pre-market database of adverse events of concern, risk management and active surveillance approaches could be developed to manage and further evaluate those concerns. In other situations where there are unexpected events, the current reporting system has been able to detect signals of an event of concern. Good pharmacovigilance requires evaluation of drug safety from many perspectives and sources. In addition, the current system depends upon the involvement of drug companies to ensure that they conduct the initial follow up that is so important for full evaluation of a report.

Enhancing the Speed and Quality of Review of Direct-to-Consumer Advertisements

CDER currently has an active program focused on the timely review of direct-to-consumer advertisements. CDER recognizes the importance of insuring that such advertisements are accurate and provide balanced information about the benefits and risks of the product. CDER is currently implementing plans to reorganize its advertising review division to improve its ability to review direct-to consumer advertisements. CDER, however, has limited resources to apply to this area in the face of an increasing number of direct-to consumer advertisements.

Grant FDA Civil Monetary Fine Authority and Subpoena Power—When companies fail to complete Phase IV confirmatory trials or when companies repeatedly violate prescriber and direct-to-consumer advertising guidelines, the agency should be given the authority to levy significant monetary penalties. The agency should also have the power to compel companies to produce relevant documents.

As part of FDAMA, Congress provided additional authority in section 21 USC 356b to monitor the progress of postmarketing studies that sponsors have agreed to conduct. Congress also instructed FDA to provide a report providing information on the status of postmarketing studies that sponsors have agreed to conduct and for which annual reports have been submitted. As indicated in the recent "Report to Congress on Reports on Postmarketing Studies," in implementing 21 USC 356b FDA has defined the content and format of annual progress reports for postmarketing studies. The Agency has also modified a number of internal operating procedures and programs to more efficiently track and monitor the status of postmarketing studies. At this time, FDA is not recommending any changes to legisla-

tive authority regarding postmarketing studies since the Administration's proposals only relate to PDUFA.

FDA has an active enforcement program to help ensure compliance with the Act and regulations governing promotion and advertising. If the Agency determines that the enforcement program governing these activities is not resulting in sufficient levels of compliance with the law, FDA will inform Congress and, if necessary, seek authority for additional penalties.

A number of provisions both in the Act and the implementing regulations enable FDA to gather information from manufacturers related to drug safety. For example, FDA's inspectional authority is set out in 21 USC 374. Under this authority, FDA is authorized to enter and inspect any factory, warehouse, or establishment where drugs are manufactured, processed, packed, or held for introduction into interstate commerce. New drug application (NDA) and abbreviated new drug application (ANDA) holders are also required to establish and maintain records and make reports to FDA of relevant data determined by FDA to be "...necessary to enable the Secretary to determine...whether there is or may be ground for invoking subsection (e)...," the provision in the Act setting forth the procedures for the withdrawal of approval of an NDA or ANDA on safety grounds. 21 USC 355(k)(1). NDA and ANDA sponsors are required to report adverse events associated with the use of a drug in human to FDA. 21 CFR 314.80. NDA and ANDA sponsors must report other safety-related information to FDA under 21 CFR 314.81. Under 21 CFE 310.305, manufacturers, packers, and distributors of marketed prescription products without NDAs or ANDAs must also report serious, unexpected adverse events to the FDA. Under the proposed PDUFA legislation, funds from user fees will be able to be expended on pre- and peri-NDA/BLA risk management plan activities. This change in the PDUFA program will help ensure that drugs approved for use in the United States continue to be among the safest in the world. As stated, if FDA determines that the tools currently in place are not adequate to maintain the high degree of drug safety in the U.S., FDA will inform Congress, and if necessary, seek additional authorities.

Launch Independent Drug Withdrawal Investigations—An office or agency independent of the FDA should investigate the circumstances surrounding the withdrawal of medical products from the market, as the National Transportation Safety Board does for plane crashes.

The complex decision to withdraw an approved product from the market requires multi-disciplinary expertise, often the same expertise critical to the decision to initially approve the product. Since FDA's mission is to protect and promote the public health, FDA believes that the creation of a separate agency to evaluate product withdrawals is unnecessary and would result in the duplication of functions that are currently being performed, and must continue to be performed, by FDA.

Increase Monitoring and Review of Phase IV Trials—Require the FDA to track Phase IV trials, strictly monitor and enforce the informed consent and protection of human subjects in those studies, and, in a timely manner, review the quality of the studies and the accuracy of the findings.

Please see response to the question relating to creating safety goals, above.

Improve Adverse Event Reporting—Hospitals, HMOs, nursing homes and other healthcare providers should be required to automatically report (the present system is voluntary) serious adverse drug events, adverse reactions and medical errors to the FDA, CDC, and/or other relevant agencies. Appropriations for FDA's oversight of adverse event reporting should be dramatically increased.

At the present time, FDA does not have authority to require hospitals, Health Maintenance Organizations (HMOs), nursing homes, and other healthcare providers to report all adverse drug events to FDA. In addition, to have all healthcare providers report every adverse event directly to FDA would overtax the system without necessarily yielding additional quality data. Part of the objective of the risk management component of the PDUFA III proposal is to develop surveillance approaches in a directed and well thought-out manner that could yield the greatest value for the particular drug. In circumstances where there are suggestions in the pre-market database of adverse events of concern, risk management and active surveillance approaches could be developed to manage and further evaluate those concerns. In other situations where there are unexpected events, the current reporting system has been able to detect signals of an event of concern. Good pharmacovigilance requires evaluation of drug safety from many perspectives and sources. The current system also depends upon the involvement of drug companies to ensure that they conduct the initial follow up that is so important for full evaluation of a report.

Utilize the Centers for Education and Research on Therapeutics—CERTS should examine the feasibility of: (1) implementing a patient self-monitoring reporting system for signaling possible adverse drug reactions; and,

(2) expanding the use of medical registries to follow patients who may be at risk of serious reactions.

FDA is currently working with the Centers for Education and Research on Therapies (CERTS) on a number of projects that relate to risk management. A current area of active work is a series of workshops that FDA, CERTS, and industry are conducting that address risk communication, risk assessment, and risk management. The objective of these workshops is the development of a research agenda to further advance the science of risk management as it relates to pharmaceuticals. In addition, the CERTS and FDA are beginning to look at the feasibility of active surveillance in emergency departments for adverse events related to drugs.

Broaden Distribution of Medication Guides—Consumers should be given power to make informed decisions about drugs and devices and to avoid preventable harm. It is time to mandate that medication guides with scientifically accurate, unbiased and clearly worded information about the risks and benefits of a treatment be included with every dispensed drug (as proposed by the FDA in 1995). Such medication guides would also, for the first time, provide a mechanism for notifying consumers directly when new safety concerns about a drug emerge that require a change in a drug's approved labeling.

As noted in the question, in 1995 FDA published a proposed rule to increase the quality and quantity of written medication information for consumers. FDA proposed requiring manufacturers to produce Medication Guides for certain medications that pose serious and significant public health concerns. In addition, the proposal encouraged that written information be produced and distributed for all drugs, and set targets for the distribution of such information with new prescriptions.

The following year a workshop was convened by FDA to discuss this proposal and, subsequent to the workshop, Congress passed legislation (P.L. 104-180) that asked interested parties to develop a plan which would attempt to achieve in a voluntary manner the goals of FDA's 1995 proposal. A plan was developed in response to the legislation that included identifying mechanisms and incentives to ensure voluntary efforts to provide useful information to consumers. The target goals established in P.L. 104-180 provided that by 2000, 75% of individuals receiving a new prescription receive useful information. By 2006 the target goal increased to 95%. FDA currently requires a Medication Guide in certain circumstances, but for most drugs the distribution of medication information to patients by a pharmacist is voluntary and is accomplished using third party vendors of such information.

Regarding the voluntary distribution of information, FDA contracted for a study of the quality and quantity of the information that was being distributed in response to the year 2000 goals. FDA is currently evaluating the results of this study and will be determining what additional actions and public discussion may be needed in an effort to ensure that the 2006 goals are achieved.

Regarding the required medication guides, these are a relatively new risk communication tool that also requires further evaluation. In particular, FDA is now working with the CERTS to develop projects evaluating the effectiveness of medication guides as a risk management tool. In addition, more study is needed of the degree to which medication guides are distributed by pharmacists and how frequently they are read and comprehended by consumers.

Section 506B of the Food, Drug, and Cosmetic Act should be amended to expand the scope of information made available to the public to include information [such] as study protocols, patient accrual rates, reports of unexpected, i.e., unlabeled, suspected adverse reactions, and study results.

As a public health agency, FDA supports making useful information available to consumers regarding the safe and effective use of regulated products. However, there are a number of considerations that must be taken into account when a determination is made to make information publicly available. Given the complex issues involved, the Agency would need to examine the language of a specific proposal in order to comment on whether or not it is advisable.

Scrutinize Single Controlled Clinical Studies—An increasing number of drug manufacturers have indicated that they will begin submitting new drug applications using data from only one controlled clinical study, which is now allowed by law, rather than multiple studies. An independent study should be conducted at an appropriate time to assess the effectiveness of single controlled studies in assessing the safety of drugs and biologics.

The usual requirement for more than one adequate and well-controlled investigation reflects the need for independent substantiation of experimental results. A single clinical experimental finding of efficacy, unsupported by other independent evidence, has not usually been considered adequate scientific support for a conclusion of effectiveness. However, FDA has, under certain circumstances, approved drugs on

the basis of development programs that included only one well-controlled clinical trial in addition to evidence from other studies that confirmed its results. The Agency issued a "Guidance for Industry: Providing Clinical Evidence of Effectiveness," in 1998 to specifically address this, as required by FDAMA. Situations in which a single controlled clinical trial might be considered adequate (in combination with confirmatory evidence) for drug approval include:

1. When the effectiveness of a new use can be extrapolated from existing studies of an already approved use (e.g., a new dosage regimen; pediatric uses).
2. When a single study for a new use is supported by data from related adequate and well controlled trials (e.g., a different phase of the same disease or a closely related disease, studies in a new special population, studies in combination or as monotherapy; studies in a closely related disease).
3. When a single controlled study includes multiple centers and is so large that it, in effect, serves as multiple studies.
4. When the endpoint and results of the single controlled study are such that the study could not ethically be repeated or the statistical results are very persuasive, with consistency across subsets of the analysis.

Although FDAMA encouraged the Agency to issue a Guidance on the subject, FDA has applied these principles for many years and continues to be actively engaged in discussions to further refine them. For example, FDA participated in a meeting convened by the Center for Drug Development Science at Georgetown University in January, 2002, entitled, "Confirmatory Evidence to Support a Single Clinical Trial (SCT) as a Basis for Drug Approval." Participants included academicians, leaders from FDA's CDER, CBER and CDRH and the pharmaceutical industry. A written summary of the conference is currently being drafted. Discussion topics included: 1) the nature, sources and standards for evidence of effectiveness; current issues concerning satisfactory requirements for "confirmatory evidence;" 2) the standards for a single clinical trial itself, and; 3) current issues in establishing an adequate safety database, assuming that effectiveness is independently confirmed.

Discussions at the meeting were constructive and productive. In general, at the meeting there was a great deal of reluctance on the part of regulators and the pharmaceutical industry, as well as many of the academicians, to apply the SCT model widely. This was felt to be a model that should only be used in limited circumstances, such as those already articulated in FDA's 1998 Guidance. It was generally acknowledged that scientifically sound clinical studies should be the goal of any drug development program, and simply conducting large numbers of poorly designed or inefficient trials is not in the interest of the public health. While most of the work at the conference centered around clarifying the principles related to the single adequate and well-controlled trial, it was widely agreed that one of the greatest needs for data at the time of NDA review is regarding safety. This point is often lost in discussions about single controlled trials and must not be, particularly in light of recent public concerns about drugs reaching the market prior to adequate safety testing.

Examine Comparative Safety Data—Manufacturers should be required, as part of their application to the FDA to market a new drug or biologic, to submit the results of tests comparing the safety and efficacy of their product to others already on the market that are used to treat the same indication.

FDA does not have the legal authority to require sponsors to submit the results of clinical trials comparing the safety and efficacy of their product to others already on the market that are used to treat the same condition. While FDA does not have this legal authority, FDA often encourages sponsors to conduct such comparative trials and in many cases the sponsors do conduct comparative trials and submit them for FDA review. If these trials meet FDA standards, the data are often included in the approved labeling for the product.

FURTHER QUESTIONS SUBMITTED BY REPRESENTATIVE JOHN D. DINGELL

Dr. Woodcock, as Director of CDER, you have the responsibility of assuring that new drugs approved under NDAs are safe. I understand that clinical trials, even ones involving thousands of patients, cannot be expected to pick up safety problems, less frequently occurring but dangerous, even fatal, side effects, is that correct?

It is correct that clinical trials would not be expected to detect rare adverse events due to the limited numbers of patients in such trials. In addition, clinical trials are limited in duration and tend to include carefully selected patient populations. For these reasons, it is critical that we maintain careful vigilance over newly marketed

drugs to be able to detect such events. The new risk management program in PDUFA III will be an important step forward toward this goal.

So safety is primarily evaluated through animal studies and pharmacokinetic models is that correct?

No. The safety of a new drug is evaluated prior to approval based on data available from a variety of studies. This includes data on how the drug is manufactured and the drug's stability over time, an analysis of safety of drug impurities, inactive ingredients, and degradation products, data from an extensive battery of animal toxicology and pharmacology studies, data from human pharmacodynamic and pharmacokinetic studies, and data from the clinical trials of the drug in humans. While the amount of safety data in humans varies depending on the drug and the indication to be treated, for chronically administered drugs, the International Conference for Harmonization (ICH) standard for the minimum size of the clinical safety database is 1,500 volunteers/patients. In many cases, FDA may require that the clinical safety database be far greater than the ICH minimum prior to approval. FDA also considers any data available from foreign post-marketing surveillance of the drug if the drug has been approved in other countries prior to approval in the United States.

I understand that CDER is working on better early measures of liver toxicity and heart toxicity both in animals and in humans so drugs that product unacceptable side effects are detected earlier in the process. Could you elaborate on you work in this area? When might we see more sensitive tests leading to greater assurance of safety at time of approval?

Regarding cardiac toxicity, FDA is addressing this issue from both the pre-clinical and clinical standpoint. FDA is working to develop guidances on appropriate preclinical assessment of drugs to screen for cardiac toxicity, in particular prolongation of the QTc interval on ECGs. This activity is still in its early stages and it may be some time before a guidance is finalized. From the clinical standpoint, FDA is working on developing guidance for industry regarding appropriate cardiac evaluation of a drug during its development. In addition, it is important for FDA to have direct access to ECG data as we evaluate drugs, and so a public meeting has been held on the topic of submitting ECG data electronically for analysis. Another public workshop is planned for this spring following which draft guidance will be developed.

Regarding hepatotoxicity, a public workshop was held in February 2001 at which time a White Paper on hepatotoxicity was written which described the issues to be addressed. These included pre-clinical, clinical and post-marketing issues. Since that time FDA has been working with industry and others to further identify the issues to be addressed and develop plans to address the various issues that are identified. These include:

- Examining the sensitivity and specificity of screening tests.
- Examining the time course and patterns of hepatotoxicity related to drugs to better inform future actions.
- Determining background rates.
- Determining the feasibility of active surveillance approaches.

FURTHER QUESTIONS SUBMITTED BY REPRESENTATIVE RICHARD BURR

When will the Agency issue the final "Guidance for Industry on Developing Medical Imaging Drugs and Biological Products"? The last draft was issued in June 2000. This Guidance is necessary in order to implement the radiopharmaceutical regulation directed by Section 122 of FDAMA which was supposed to be effective almost 3 years ago under FDAMA.

The guidance for industry on Developing Medical Imaging Drugs and Biological Products is being developed with extensive input from the public. A first draft of the guidance was issued for comment on October 14, 1998. FDA held public meetings on the draft guidance on January 25 and March 26, 1999. After considering the discussion and comments at the meetings and after reviewing all written comments, FDA issued a second draft for comment on July 31, 2000. The Agency has considered carefully the second round of comments, and the final version of the guidance is currently moving through the clearance process. We expect it to be released during the next month or two.

FURTHER QUESTIONS SUBMITTED BY REPRESENTATIVE HENRY A. WAXMAN

It is my understanding that FDA has fewer than 15 FTEs to review over 37,000 prescription drug ads each year, and the triggers in the user fee program have been partly to blame because FDA has been forced to drain resources from other programs, including drug advertising, to meet its obli-

gations under PDUFA. In your best professional judgment, how many FTEs would be needed and how much would it cost to fund an effective drug advertising review program and bring enforcement actions against misleading ads in a timely manner?

The Division of Drug Marketing and Advertising (DDMAC) in CDER is responsible for the regulation of prescription drug advertising. This Division currently has assigned 39 FTEs. While DDMAC has worked to maximize its productivity and is currently undergoing a reorganization that is designed to further improve its efficiency and effectiveness, the current staffing is not adequate to keep pace with the rapidly increasing number of professional and direct-to-consumer advertisements for prescription drugs. It is estimated that CDER would need approximately 35 additional FTEs and supporting operating funds to fully staff the advertising review program.

Currently, CBER has 4 FTEs to review all advertising and promotional labeling materials submitted. In order to adequately assess these materials and bring timely enforcement actions, a large increase in staff would be required. Based on the projected number of submissions for FY2003, and conservative estimates of man-hours needed to review these submissions, 30 additional review FTEs would be required. Additional management and support staff would also be needed, for a total of 38 FTEs at a cost of $5,130,000.00. An additional $550,000 would be required for IT upgrade and support of a tracking system. This would result in a total requirement of $5,680,000.00.

Have statutory triggers in PDUFA adversely affected funding of other FDA programs? If so, which ones?

As is mentioned above, during the period of FY 1994 to FY 2001, the effect of the Prescription Drug User Fee Act's (PDUFA) statutory triggers has had on the availability of funding for non-PDUFA programs has been less significant than the absence of additional appropriations to fund that annual pay raises for Food and Drug Administration (FDA) employees. During these years, FDA's appropriations failed to include increases to cover the annual costs of mandated Federal pay raises. The cumulative impact of absorbing the cost of the Federal pay raise during this eight-year period was more than $200 million. This resulted in a reduction in staffing for programs other than the process for the review of human drug applications (e.g., compliance activities, review of over-the-counter drugs) of more than 1,100 staff years since PDUFA I was enacted.

Although the absence of additional funds to pay the cost of mandated pay raises has had the greatest effect on non-PDUFA programs, one of the PDUFA triggers has also had a significant effect. Section 736(g)(2)(B) requires that FDA annual spending on drug review from appropriations must be at least as much as the amount of appropriations that FDA spent on drug review in FY 1997, adjusted for inflation.

There are two aspects of this trigger that may adversely affect FDA programs other than drug review. These are:

(1) The minimum that FDA must spend from appropriations increases by an inflation factor each year. In years when FDA does not receive appropriated increases to cover the cost of the Federal pay raise, FDA must increase the amount allocated for PDUFA drug review programs by an amount sufficient to meet the adjustment for inflation established in the PDUFA statute. The only means of accomplishing this is to reduce the amount spent on non-PDUFA programs. This aspect of the section 736(g)(2)(B) trigger is directly related to whether or not FDA receives the appropriations necessary to cover the cost of the Federal pay raise.

(2) This trigger is based on FDA spending, an amount that cannot be measured until after the fiscal year ends, when the accounts are closed and final reports are produced. Failure to meet this spending threshold would be catastrophic. Fee revenue collected in the previous year would all have to be returned and this loss in revenue would mean that FDA would have to lay off a significant number of employees. To avoid these catastrophic consequences, FDA must always err on the side of caution by spending more on the drug review process than the minimum amount required. This is necessary to be certain that, when the final accounting is completed at the end of the year, FDA will have met the minimum spending required.

The table below outlines this situation. It depicts:

(1) the minimum amount of spending required from appropriations each year as a result of this trigger (Section 736(g)(2)(B));

(2) the actual FDA spending from appropriations each year on the drug review process; and

(3) the amount by which FDA spending exceeded the minimum spending mandated by the statutory trigger (i.e., the difference between 1 and 2.)

Fiscal Year	Minimum Spending Required by Section 736(g)(2)(B)	Actual Spending from Appropriations	Difference	Percent Difference
1993	$120,057,253	$126,515,577	$6,458,324	5
1994	$123,380,438	$129,337,138	$5,956,700	5
1995	$126,958,144	$139,830,318	$12,872,174	10
1996	$124,302,476	$152,289,387	$27,986,911	23
1997	$125,872,166	$147,959,689	$22,087,523	18
1998	$147,959,689	$151,836,635	$3,876,946	3
1999	$150,083,954	$159,669,575	$9,585,621	6
2000	$153,508,177	$167,646,122	$14,137,945	9
2001	$158,213,295	$162,691,657	$4,478,362	3

Will your recommended alteration in one of the triggers ensure that funding for other programs is no longer drained?

The most important action to assure that funding from other programs is not drained in the future is an appropriation each year that includes the full costs of the mandatory Federal pay raise. We are pleased that for the current fiscal year the President requested, and Congress appropriated, funds that specifically included amounts to enable FDA to meet the costs of the mandatory Federal pay increase. Further, the President's budget for FY 2003 that is now before Congress also includes specific increases to cover the cost of the mandatory Federal pay raise anticipated in FY 2003.

In addition, the legislation that the Administration has proposed will include modifications to the trigger (Section 736(g)(2)(B)) such that FDA will no longer be compelled to spend amounts that are significantly greater than the amount required by this trigger. The proposal will provide FDA a margin of error in its effort to meet this requirement of the law. Under this proposed modification, if FDA's spending from appropriations on drug review is within 5 percent of the amount required by this section of the law, the requirement is considered to be satisfied. In cases where FDA's spending from appropriations is within 3 percent of the trigger amount, no adjustment in fees will be required. If the spending is between 3 percent and 5 percent below the trigger amount, then FDA will, in a subsequent year, decrease user fees by the amount of the shortfall that is between 3 and 5 percent (i.e., a maximum of 2 percent).

The purpose of this change is to relieve FDA of the need to overspend from appropriations each year, as has occurred consistently since FY 1994. Spending from appropriations on the drug review process each year is still expected to be at, or very close to, the amount specified by this trigger, and may never be more than 5 percent below the trigger amount.

What changes in the triggers would be necessary to protect the funding of the generic drug and advertising review programs?

The PDUFA statute does not apply to generic drugs or to post-approval drug advertising. Since there are no user fee or non-user fee amounts authorized for these programs under the PDUFA statute, it is difficult to conceive of a modification to the PDUFA statute that would accomplish this objective.

The best way to protect funding for these and other non-PDUFA programs is to assure that they receive adequate appropriations each year, including increases to cover the costs of mandatory Federal pay raises.

In your best professional judgment, how many FTEs would be needed and how much would it cost to fund a generic drug program that can review generic drug applications in the statutory 180 days.

It is estimated that the Office of Generic Drugs (OGD) would need approximately 55 additional FTEs at a cost of $9,570,000 above its current base to meet the statutory review time of 180 days. This amount includes salary, operating costs, and overhead to support these additional employees.

In addition, other parts of the Agency, such as the Office of Compliance, CDER, and FDA's Office of Regulatory Affairs and Office of Chief Counsel, would need additional FTEs and budgetary support. These other organizations provide essential inspection and legal support to OGD's review activities. It is estimated that an additional 66 FTEs would be needed to cover the increased workload in these organizations in support of the Office of Generic Drugs for a total of $20,430,000. This figure includes salary, operating costs, and overhead.

As I understand it, your agreement with the pharmaceutical industry will include a performance goal of 6 months for reviewing any portion of a cu-

mulative marketing application. This is the same review period as a priority drug; hence these partial applications are going to be given as high as priority as priority drugs. I am concerned that this will take resources away from needed drugs that are ready for approval, and give them to drugs that may be far from approval. Does your agreement include sufficient additional fees to cover the cost of carrying out these additional high priority reviews? Can we be sure that resources will not be diverted from the review of drugs that are ready for approval to review CMAs?

FDA carefully considered the resources that would be necessary to implement the two pilot studies of continuous marketing application (CMA) review without taking resources away from the review of completed new drug applications. The necessary resources have been included in the PDUFA III proposals. It is also important to note that both pilot CMA programs will be limited to Fast Track drugs—those drugs that are intended to treat serious or life-threatening conditions and that demonstrate the potential to address unmet medical needs. Additionally, Pilot 1 is limited to Fast Track drugs that have already demonstrated significant promise as a therapeutic advance in clinical trials and Pilot 2 is limited to one application per review division over the five-year period of PDUFA III. FDA believes the additional resources and the limitations on the CMA pilot program will provide opportunities to shorten drug development time for promising new drugs, while ensuring appropriate resources are devoted to other new drugs that are ready for approval. FDA proposes to conduct a formal evaluation of these Pilot programs during PDUFA III in order to evaluate these and other considerations.

After FDA has completed a review of a portion of a cumulative marketing application, is the agency free to rereview all or part of that portion when the full application is submitted, if the agency believes a rereview is needed?

Yes. FDA plans to publish a guidance to industry on the cumulative marketing application pilot programs by the end of FY03 and the pilot programs will begin in FY04. FDA anticipates that the guidance document will outline the procedures that FDA will follow with regard to any changes that may occur to a "reviewable unit" from the time that it was pre-submitted for review until the time that the complete application is submitted. The pilot programs described in the PDUFA III proposed Goals Letter do not preclude FDA from re-reviewing previously reviewed "reviewable units" if that is felt to be necessary. The pilot programs as described in the draft Goals Letter also make clear that the deficiencies transmitted to the sponsor in a discipline review letter on completion of review of a pre-submitted "reviewable unit" are "not final, definitive decisions relevant to the NDA/BLA."

At the hearing, the witnesses representing BIO testified that, under the agreement, the decision whether to use an outside expert requested by an applicant is completely within FDA's discretion. I was pleased to hear this, because I believe that restricting FDA's discretion raises serious questions about the integrity of the review process. What are the specific terms in the agreement concerning the use of outside experts that establish FDA's discretion to use them as the agency sees fit?

Section IX of the Goals Letter provides for the use of independent consultants for biotechnology clinical trial protocols. The text of this section of the Goals Letter is reprinted below.

IX. INDEPENDENT CONSULTANTS FOR BIOTECHNOLOGY CLINICAL TRIAL PROTOCOLS

A. Engagement of Expert Consultant: During the development period for a biotechnology product, a sponsor may request that FDA engage an independent expert consultant, selected by FDA, to participate in the Agency's review of the protocol for the clinical studies that are expected to serve as the primary basis for a claim.

B. Conditions

1. The product must be a biotechnology product (for example, DNA plasmid products, synthetic peptides of fewer than 40 amino acids, monoclonal antibodies for in vivo use, and recombinant DNA-derived products) that represents a significant advance in the treatment, diagnosis or prevention of a disease or condition, or have the potential to address an unmet medical need;

2. The product may not have been the subject of a previously granted request under this program;

3. The sponsor must submit a written request for the use of an independent consultant, describing the reasons why the consultant should be engaged (e.g., as a result of preliminary discussions with the Agency the sponsor expects substantial disagreement over the proposed protocol); and

4. The request must be designated as a "Request for Appointment of Expert Consultant" and submitted in conjunction with a formal meeting request (for example, during the end-of-Phase II meeting or a Type A, meeting).

C. Recommendations for Consultants: The sponsor may submit a list of recommended consultants for consideration by the Agency. The selected consultant will either be a special government employee, or will be retained by FDA under contract. The consultant's role will be advisory to FDA and FDA will remain responsible for making scientific and regulatory decisions regarding the clinical protocol in question.

D. Denial of Requests: Except in the most unusual circumstances (for example, it is clearly premature) FDA will honor the request and engage the services of an independent consultant, of FDA's choosing, as soon as practicable. If the Agency denies the request, it will provide a written rationale to the requester within 14 days of receipt.

E. Performance Goal Change: Due to the time required to select and screen the consultant for potential conflicts of interest and to allow the consultant sufficient time to review the scientific issues involved, the performance goals for scheduling the formal meeting (see section III) may be extended for an additional sixty (60) days.

F. Evaluation: During FY 2006, FDA will conduct a study to evaluate the costs and benefits of this program for both sponsors and the Agency.

U.S. Food and Drug Administration

EXECUTIVE SUMMARY

MANAGING THE RISKS FROM MEDICAL PRODUCT USE

CREATING A RISK MANAGEMENT FRAMEWORK

REPORT TO THE FDA COMMISSIONER
FROM THE TASK FORCE ON RISK MANAGEMENT

U.S. Department of Health and Human Services
Food and Drug Administration
May 1999

Executive Summary

As one of her first initiatives after being sworn in as FDA Commissioner, Dr. Jane Henney established a Task Force to evaluate the system for managing the risks of FDA-approved medical products, focusing particularly on FDA's part in the system. This report is the result of that review.

Briefly, the Task Force assessed risk management practices within the overall healthcare delivery system, focusing on the roles and responsibilities of each participant. The Task Force applied a risk management model used in other Federal sectors. We also examined the various risks from medical products and their sources. The Task Force then evaluated FDA's role in the current system. First, we reviewed the Agency's ***premarketing*** risk assessment and approval processes to determine if serious adverse events are occurring at a higher rate now than they have in the past. Next, the Task Force evaluated FDA's ***postmarketing*** surveillance and risk assessment programs to see if they are doing the job they were intended to do. Finally, the Task Force analyzed all of FDA's risk management activities to evaluate the Agency's role in the overall system for managing medical product risks. Our findings are summarized here.

Return to Table Contents

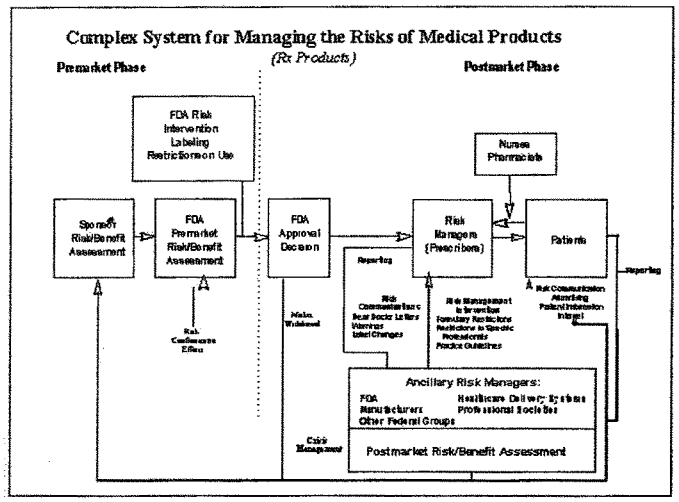
FINDINGS

The time is right for a new framework

The key finding of our review is that the time is right to apply a systems framework to medical product risk management. The FDA plays only a part in the complex system of risk management. Numerous other groups participate in decision making related to the use of medical products. A systems framework for risk management should enable a better integration of the efforts of all the involved parties. Such a framework also should facilitate a better understanding of both the risks involved in using medical products and the sources of those risks. A better understanding of risks and a more integrated risk management system will enable more effective risk interventions.

The current risk management system has evolved over time

At the turn of this century, healthcare in this country was generally provided by a family practitioner who treated patients from cradle to grave. As illustrated in the following figure, medical products today are developed and used within a complex system involving a number of key participants: (1) manufacturers who develop and test products and submit applications for their approval to the FDA; (2) the FDA, which has an extensive premarketing review and approval process and uses a series of postmarketing surveillance programs to gather data on and assess risks; (3) other participants in the healthcare delivery system, including healthcare practitioners; and (4) patients, who rely on the ability of this complex system to provide them with needed interventions while protecting them from injury.

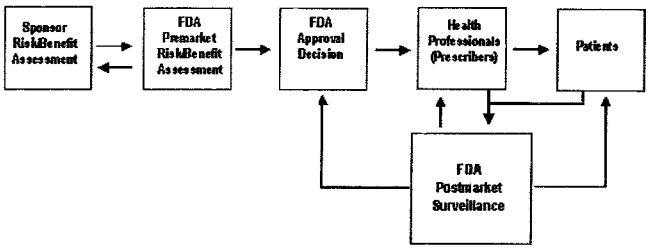


Not everyone's role is clearly defined

Although medical products are required to be safe, safety does not mean zero risk. A safe product is one that has reasonable risks, given the magnitude of the benefit expected and the alternatives available. All participants in the medical product development and delivery system have a role to play in maintaining this benefit-risk balance by making sure that products are developed, tested, manufactured, labeled, prescribed, dispensed, and used in a way that maximizes benefit and minimizes risk. In some cases, roles are clearly defined. For example, FDA's current efforts, which are laid out in the Federal Food, Drug, and Cosmetic Act, are largely devoted to pre- and postmarketing risk assessment. The FDA approval/nonapproval decision is the Agency's central risk management action. FDA must ensure that beneficial medical products are available and labeled with adequate information on their risks and benefits while protecting the public from unsafe products or false claims. The figure below is a snapshot of FDA's role in the current risk management system. During premarketing review, the Agency assesses the evidence demonstrating the benefits and describing the risks of medical products.

FDA Role in Medical Products Risk Management

(Rx Products)

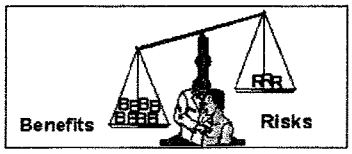


The Agency approves a product when it judges that the benefits of using a product outweigh the risks for the intended population and use. A major goal of the premarketing review is to ensure that products are truthfully and adequately labeled for the population and use. Labeling is given considerable emphasis because it is the chief tool the Agency uses to communicate risk and benefit to the healthcare community and patients.

Once medical products are on the market, however, ensuring safety is principally the responsibility of healthcare providers and patients, who make risk decisions on an individual, rather than a population, basis. They are expected to use the labeling information to select and use products wisely, thereby minimizing adverse events.

FDA
evaluates benefits/risks for the population

Provider
evaluates benefits/risks for a patient



Patient
evaluates benefits/risks in terms of personal values

To assist with postmarketing risk management, the Agency maintains a system of complex postmarketing surveillance and risk assessment programs to identify adverse events that are not identified during medical product development and premarketing review. FDA monitors suspected adverse events associated with the use of an approved medical product. The Agency uses this information to initiate labeling updates and, on rare occasions, to reevaluate the marketing decision.

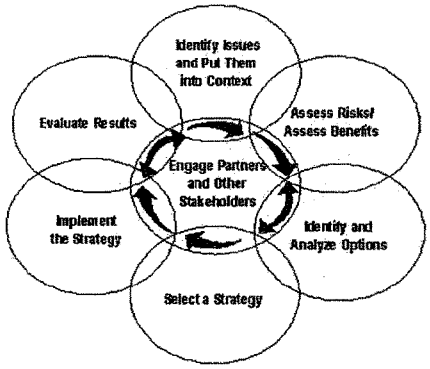
Although the FDA's role is fairly clear, the roles of some of the other participants are less clear. This is because what began as individualized care by one practitioner has evolved into a complex system of risk management that now involves manufacturers, the FDA, practitioners, many other elements of the healthcare delivery system, and patients. With the flood of new products reaching the marketplace, an increasingly complex healthcare environment, and the emerging global market, the Task Force believes that a new conceptual framework for risk management activities is needed. The new framework should help define the roles of those involved and better integrate their efforts.

How would a new systems framework look?

As discussed in Part 4, a specific model has been developed for managing the risks

associated with other health and safety issues within the Federal Government.[1] This model encompasses the basic processes that are used to identify and assess the risks of specific health hazards, implement activities to eliminate or minimize those risks, communicate risk information, and monitor and evaluate the results of the interventions and communications. The Task Force found that the processes identified in the Federal model are consistent with the activities the Agency and many of the other involved participants currently undertake as part of their approach to risk management. Under the current system, however, these activities are fragmented, rather than part of an integrated systems effort. The Task Force easily adapted the Federal model to create a proposed model for managing the risks associated with using medical products. (See the proposed model below.) This new framework encourages a much greater integration of risk management efforts than the current system.

Proposed Risk Management Model



One activity often missing from other risk management models that is implicit in risk-benefit assessment and is critical in a system that would manage healthcare risks involves engaging healthcare partners and other stakeholders in risk-benefit analyses. This activity is characterized by others as ***risk confrontation:*** community-based problem solving that actively involves relevant stakeholders in

the decision-making process. [2] This is one area of activity that traditionally has had lower priority in the Agency than its pre- and postmarketing scientific risk assessment responsibilities. The Task Force believes that risk confrontation is a key process that needs to be a part of any new risk management framework.

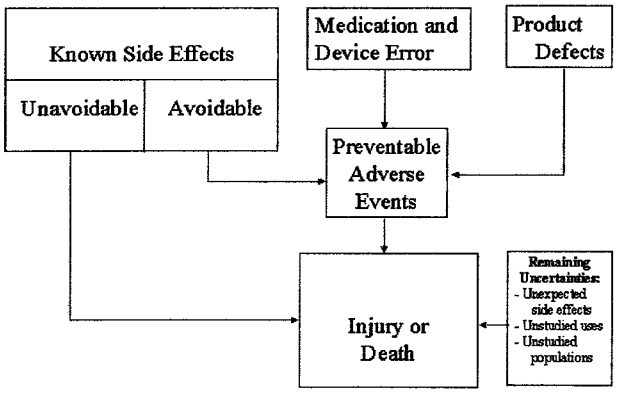
FDA should engage stakeholders to examine the current risk management system

The Task Force recommends that FDA take the opportunity to engage all stakeholders to reexamine the current system for managing the risks associated with the use of medical products. We encourage a public policy discussion that focuses on defining more clearly the roles and responsibilities of all participants of the risk management system -- FDA, industry, healthcare provider organizations, healthcare practitioners, patients, and the public. Only by examining the roles of these various participants can gaps and misallocation of efforts be identified and improvements made.

Understanding the types of risks and their sources is critical

To evaluate the current system, it is critical that the stakeholders also consider what is known about the sources of risk from medical products and what is not yet completely understood. As discussed in detail in Part 1 of the report, risks from medical products generally fall into four categories.

Sources of Risk From Medical Products



Most injuries and deaths associated with the use of medical products result from their ***known side effects***. Some side effects are unavoidable, but others can be prevented or minimized by careful product choice and use. It is estimated that more than half of the side effects from pharmaceuticals are avoidable.[3] Other sources of preventable adverse events are ***medication or device errors***. Injury from ***product defects*** is unusual in the United States because of the great attention paid to product quality control and quality assurance during manufacturing. The final category of potential risk involves the ***remaining uncertainties*** about a product.

Knowledge about a product will always be limited to some extent at the time of approval by factors in the product development process. For example, rare side effects and long-term outcomes (both positive and negative) may not be known when a product is approved because of the relatively small size and short duration of clinical trials. And because of the populations not studied in clinical trials (e.g., pregnant patients, children, people with other diseases) or minimally studied (e.g., geriatric patients), side effects may be discovered if these groups are treated with a product after it goes on the market. Even after long use of a product, uncertainties will remain.

One problem for discussion is the lack of adequate data about the causes, incidences, preventability, and relative contribution of the various types of risk. Currently, no group has the role of collecting and analyzing these types of data. Systematic approaches to risk management require the use of such data to plan and evaluate the success of risk interventions. It is unlikely that major improvements in risk management can occur without better data.

All participants in the risk management system, including the FDA, have a role to play in minimizing the risks from using marketed medical products. The Task Force believes that the stakeholders should collaborate to determine how better data on risks can be collected - so that efforts and interventions can be targeted to the most serious problems, and the effects of interventions can be evaluated.

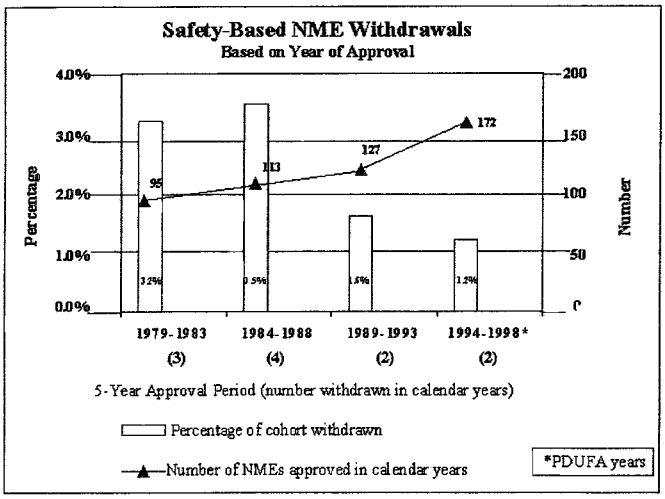
FDA's current role in risk management

Turning to FDA's role in overall risk management, the Task Force examined the Agency's premarketing and postmarketing risk assessment activities, evaluating their quality and effectiveness. The Task Force also looked at FDA's efforts in other aspects of risk management such as risk communication, confrontation, and overall evaluation.

As discussed in detail in Part 2 of this report, the Task Force evaluated whether the heightened sense of time pressure on Agency review teams has reduced the quality of FDA's premarketing reviews or caused poor decision making. We studied how often previously unanticipated serious adverse events[4] were identified after approval in drugs reviewed since the implementation, beginning in 1990, of several legislative (e.g., PDUFA) and managerial initiatives to speed the Agency's review process.[5] We then compared the numbers to those collected by a 1990 General Accounting Office (GAO) report on serious adverse events for drugs reviewed prior to 1990.[6] We also examined FDA's quality control systems for premarketing review and marketing decisions to see if adequate systems are in place.

Rates of withdrawals and adverse events remain low

We found that FDA's premarketing review processes are successfully identifying the serious risks associated with using medical products at least as well as in previous decades. Despite shortened FDA review time, comparisons of drugs reviewed and approved during the 1990s to those approved previously show that the rate of market withdrawals for safety reasons has remained relatively unchanged over the decades. As the graph below shows, the rate of safety-based market withdrawals of new molecular entities (NMEs) has ranged from approximately 1 to 3.5 percent over the past several decades.[7]



With advances in scientific knowledge, safety problems may be identified for long-marketed products. For example, of the five drugs withdrawn for safety reasons after 1992, two were approved before PDUFA was implemented.[8] In addition, comparisons also showed that unexpected serious adverse events resulting in revisions to product labeling after approval are occurring proportionately less often than in the past.

The Task Force also found that the key elements of an International Standards Organization (ISO)-modeled quality assurance/quality control program for premarketing review are in place and being used. FDA has consistently used supervisory rereview, conducted by subject matter experts, for 100 percent of the marketing decisions as the cornerstone of its quality control function. These quality control reviews are conducted typically at three supervisory levels before a final approval decision is made.

Some factors limit the identification of adverse events

The Task Force analysis identified several factors in the medical product development process that limit the Agency's ability to observe some kinds of adverse events before marketing. Factors include the relatively small size and

short duration of clinical trials and the representativeness of the patients studied. For example, as discussed in Part 2, rare side effects are often not observed before marketing because of the limited number of patients exposed to a product before approval. And, most trials do not last long enough to enable identification of potential long-term side effects. In addition, patients in clinical trials are often not representative of the types of people who will be exposed to a product once it goes on the market. Changing these aspects of medical product development could increase the manufacturers' and the Agency's ability to identify serious risks before marketing. However, such changes would increase development costs and slow product availability.

Finally, the Task Force believes that in the case of some new medical products, consideration should be given to how rapidly they are made available in the marketplace for widespread use. Slowing a rapid market rollout for some products when time-tested alternatives are available could limit the impact of unexpected serious adverse events.

Postmarketing surveillance and risk assessment are performing as designed

We found that the postmarketing surveillance programs currently in place are good at rapidly detecting most unexpected serious adverse events that occur during the postmarketing period. As described in more detail in Part 3 of this report, the Agency relies principally on a ***passive*** adverse event reporting system, depending to a great extent on voluntary reporting by the healthcare community. The system rapidly alerts the Agency to the occurrence of rare, serious adverse events not previously identified.

The system also provides an increased understanding of the range of severity in known product-associated adverse side effects. We found that the Agency's postmarketing surveillance and risk assessment programs are performing well for the goals they were designed to achieve. However, FDA's programs were not designed to evaluate the rate, or the impact, of known adverse events.

The Task Force has presented some options for expanding the use of automated systems for reporting, monitoring, and evaluating adverse events and product defects and increasing the Agency's access to data sources that would supplement and extend its passive reporting systems. These would enhance the Agency's ability to evaluate reports of serious adverse events. Examples of such sources include broad-based health information databases and data from sentinel user facilities where staff are trained to rapidly recognize and accurately report adverse events. Implementing some of these changes would require increased funding.

Return to Table of Contents

CONCLUSIONS, RECOMMENDATIONS, AND OPTIONS

Conclusions

Medical products provide great benefit to the public, but they can also cause injury. FDA and the many other participants in healthcare delivery act to maximize the benefits and minimize the risks associated with using medical products, but often the actions of the participants are insufficiently integrated. The Task Force believes that the common goal of maximizing benefits and minimizing risks could be greatly advanced if the participants in the system worked together to gain an understanding of these activities within a systems framework. To achieve such a framework, we need a better understanding of the risks involved and their sources, and we need to clarify our individual roles and ensure that our individual roles are well integrated. Only then can we plan effective risk management strategies.

The Task Force also examined in detail FDA's role in the overall system. We find that the Agency's pre- and postmarketing risk assessment systems are performing well. Nonetheless, we believe that additional emphasis should be placed on the quality assurance of our premarketing review programs. In addition, the Task Force finds that program expansion is needed to ensure that our postmarketing programs are able to meet the challenges of the current regulatory and healthcare environment.

Recommendations

The Task Force is making a number of recommendations as a result of its review. Most recommendations center around ways that FDA, within the confines of the current system, can further improve its risk management activities. The Agency intends to implement these recommendations. Many of these improvements already are underway, and the Task Force recommends that ongoing enhancements be aggressively pursued. Specifics can be found at the end of Parts 2, 3, and 4 of the report, but these recommendations generally include:

- Initiate steps to have each Center establish separate quality assurance/quality control units.
- Ensure and document ongoing professional education and core competency training for all reviewers.
- Complete the good review practice documents and keep them current.
- Rapidly complete AERS and enhance MAUDE adverse event reporting systems for pharmaceutical products and medical devices.
- Integrate existing postmarketing systems so analytical tools, data entry, and editing can be uniformly applied, and all information is readily available to every reviewer.

- Enhance and intensify surveillance of newly marketed products.
- Develop new methodological tools for inference from available datasets.

The Task Force also identified a number of options for consideration, which, if adopted, might contribute to improved risk management. These ideas need full public policy analysis and review to understand their potential value, costs, and acceptability to the various stakeholders in medical product risk management. Some of the options would require significant new resources and legislative changes. Input from stakeholders on these options and their prioritization is needed. For these reasons, the Task Force's key recommendation is that:

- FDA join in or convene a meeting, or series of meetings, with stakeholders to discuss the current system for managing risks. As part of this meeting, FDA should consult stakeholders about the options identified in detail in the report and summarized below.

Options

The Task Force identified a number of options that we believe may improve the FDA's risk management activities as well as improve the overall system of managing the risks from medical products. These options should be evaluated in the context of the stakeholder risk confrontation meeting(s) recommended above. Only by working with all other participants in the overall risk management system for medical products can the Agency arrive at the most effective approach for managing those risks.

Details of the options for public consideration can be found in the relevant chapters of this report. In summary, these options might include:

- Examine and evaluate mechanisms designed to address the inherent limits of premarketing development (e.g., wider use of large, community-based simple trials, restricting exposure during the early postmarketing period).
- Design and implement additional mechanisms to obtain postmarketing information (e.g., sentinel sites, prospective product use registries, enhanced links to external databases).
- Enhance Agency epidemiological and methodological research activities.
- Enhance the Agency's role and responsibilities in risk communication.
- Increase the number of postmarketing risk interventions for products with special risks, such as restricting distribution of products or requiring mandatory educational programs for healthcare professionals and patients.
- Seek legislative changes for other types of risk intervention, such as suspension authority for drugs.

Footnotes

[1] *Presidential/Congressional Commission on Risk Assessment and Risk Management, Framework for Environmental Health Risk Management - Final Report, Vol. 1, 1997.*

[2] *Leviton, L.C., C.E. Needleman, and M.A. Shapiro, Confronting Public Health Risks: A Decision Maker's Guide, SAGE Publications, Inc., 1998.*

[3] *Bates, D.W., L.L. Leape, and S. Petrycki, "Incidence and Preventability of Adverse Drug Events in Hospitalized Adults," J Gen Intern Med., 8:289-294, 1993.*

[4] *A number of terms are used to describe an adverse event, including adverse drug reaction (ADR), adverse experience, and adverse effect. In this report, the term adverse event is used in most cases to avoid confusion.*

[5] *Through the Prescription Drug User Fee Act of 1992 (PDUFA) and the Food and Drug Administration Modernization Act of 1997, Congress has encouraged the FDA to act more rapidly in making decisions on whether new medical products may enter the marketplace.*

[6] *Government Accounting Office, FDA Drug Review - Postapproval Risks 1976 - 1985, GAO/PEMD-90-15, April 1990.*

[7] *FDA, Center for Drug Evaluation and Research, 1998 Report to the Nation, May 1999.*

[8] *Redux, Pondimin, Seldane, Duract, and Posicor were withdrawn from the market in 1997 and 1998; Seldane and Pondimin were approved prior to PDUFA. For a full discussion, see Friedman, M.A., J. Woodcock, M. Lumpkin, J. Shuren et al., "The Safety of Newly Approved Medicines: Do Recent Market Removals Mean There is a Problem?" JAMA, Vol. 281, No. 18, May 12, 1999.*

Return to Table of Contents

U.S. Food and Drug Administration

ENCLOSURE

PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES

The performance goals and procedures of the FDA Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER), as agreed to under the reauthorization of the prescription drug user fee program in the [cite statute] are summarized as follows:

I. REVIEW PERFORMANCE GOALS - FISCAL YEAR 2003 THROUGH 2007

A. NDA/BLA Submissions and Resubmissions:

Review and act on 90 percent of standard original NDA and BLA submissions filed during fiscal year within 10 months of receipt.

1. Review and act on 90 percent of priority original NDA and BLA submissions filed during fiscal year within 6 months of receipt.

2. Review and act on 90 percent of Class 1 resubmitted original applications filed during fiscal year within 2 months of receipt.

3. Review and act on 90 percent of Class 2 resubmitted original applications filed during fiscal year within 6 months of receipt.

Original Efficacy Supplements:

1. Review and act on 90 percent of standard efficacy supplements filed during fiscal year within 10 months of receipt.

2. Review and act on 90 percent of priority efficacy supplements filed during fiscal year within 6 months of receipt.

Resubmitted Efficacy Supplements:

Fiscal Year 2003:

1. Review and act on 90 percent of Class 1 resubmitted efficacy supplements filed during fiscal year 2003 within 6 months of receipt and review and act on 30 percent within 2 months of receipt.

2. Review and act on 90 percent of Class 2 resubmitted efficacy supplements filed during fiscal year 2003 within 6 months of receipt.

Fiscal Year 2004:

1. Review and act on 90 percent of Class 1 resubmitted efficacy supplements filed during fiscal year 2004 within 4 months and review and act on 50 percent within 2 months of receipt.

2. Review and act on 90 percent of Class 2 resubmitted original applications filed during fiscal year 2000 within 6 months of receipt.

Fiscal Year 2005:

1. Review and act on 90 percent of Class 1 resubmitted efficacy supplements filed during fiscal year 2005 within 4 months of receipt and review and act on 70 percent within 2 months of receipt.

2. Review and act on 90 percent of Class 2 resubmitted efficacy supplements within 6 months of receipt.

Fiscal Year 2006

1. Review and act on 90 percent of Class 1 resubmitted efficacy supplements filed during fiscal year 2006 within 4 months of receipt and review and act on 80 percent within 2 months of receipt.

2. Review and act on 90 percent of Class 2 resubmitted efficacy supplements within 6 months of receipt.

Fiscal Year 2007:

1. Review and act on 90 percent of Class 1 resubmitted efficacy supplements filed during fiscal year 2007 within 2 months of receipt.

2. Review and act on 90 percent of Class 2 resubmitted efficacy supplements within 6 months of receipt.

Original Manufacturing Supplements:

1. Review and act on 90 percent of manufacturing supplements filed during fiscal year within 6 months of receipt and review and act on 90 percent of manufacturing supplements requiring prior approval within 4 months of receipt.

These review goals are summarized in the following tables:

ORIGINAL and RESUBMITTED NDAs/BLAs:

SUBMISSION COHORT	STANDARD	PRIORITY
Original Applications	90% IN 10 MO	90% IN 6 MO
Class 1 Resubmissions	90% IN 2 MO	90% IN 2 MO
Class 2 Resubmissions	90% IN 6 MO	90% IN 6 MO

ORIGINAL and RESUBMITTED EFFICACY SUPPLEMENTS:

SUBMISSION COHORT	STANDARD	PRIORITY
Original Efficacy Supplements	90% In 10 MO	90% IN 6 MO

RESUBMITTED EFFICACY SUPPLEMENTS

SUBMISSION COHORT	CLASS 1	CLASS 2
FY 2003	90% IN 6 MO/30% IN 2 MO	90% IN 6 MO
FY 2004	90% IN 4 MO/50% IN 2 MO	90% IN 6 MO
FY 2005	90% IN 4 MO/70% IN 2 MO	90% IN 6 MO
FY 2006	90% IN 4 MO/80% IN 2 MO	90% IN 6 MO
FY 2007	90% IN 2 MO	90% IN 6 MO

MANUFACTURING SUPPLEMENTS

SUBMISSION COHORT	MANUFACTURING SUPPLEMENTS NO PRIOR APPROVAL ("CHANGES BEING EFFECTED" OR "30-DAY SUPPLEMENTS")	MANUFACTURING SUPPLEMENTS THAT DO REQUIRE PRIOR APPROVAL
FY 2003 – 2007	90% IN 6 MO	90% IN 4 MO

II. NEW MOLECULAR ENTITY (NME) PERFORMANCE GOALS

A. The performance goals for standard and priority original NMEs in each submission cohort will be the same as for all of the original NDAs (including NMEs) in each submission cohort but shall be reported separately.

B. For biological products, for purposes of this performance goal, all original BLAs will be considered to be NMEs.

III. MEETING MANAGEMENT GOALS

A. Responses to Meeting Requests

1. Procedure: Within 14 calendar days of the Agency's receipt of a request from industry for a formal meeting (i.e., a scheduled face-to-face, teleconference, or videoconference) CBER and CDER should notify the requester in writing (letter or fax) of the date, time, and place for the meeting, as well as expected Center participants.

2. Performance Goal: FDA will provide this notification within 14 days for 90% in FY 2003 - 2007.

B. Scheduling Meetings

1. Procedure: The meeting date should reflect the next available date on which all applicable Center personnel are available to attend, consistent with the component's other business; however, the meeting should be scheduled consistent with the type of meeting requested. If the requested date for any of these types of meetings is greater than 30, 60, or 75 calendar days (as appropriate) from the date the request is received by the Agency, the meeting date should be within 14 calendar days of the date requested.

   Type A Meetings should occur within 30 calendar days of the Agency receipt of the meeting request.

   Type B Meetings should occur within 60 calendar days of the Agency

receipt of the meeting request.

Type C Meetings should occur within 75 calendar days of the Agency receipt of the meeting request.

2. Performance goal: 90% of meetings are held within the timeframe (based on cohort year of request) from FY 03 to FY 07.

C. Meeting Minutes

1. Procedure: The Agency will prepare minutes which will be available to the sponsor 30 calendar days after the meeting. The minutes will clearly outline the important agreements, disagreements, issues for further discussion, and action items from the meeting in bulleted form and need not be in great detail.

2. Performance goal: 90% of minutes are issued within 30 calendar days of date of meeting (based on cohort year of meeting) in FY 03 to FY 07.

D. Conditions

For a meeting to qualify for these performance goals:

1. A written request (letter or fax) should be submitted to the review division; and

2. The letter should provide:

   a. A brief statement of the purpose of the meeting;

   b. A listing of the specific objectives/outcomes the requester expects from the meeting;

   c. A proposed agenda, including estimated times needed for each agenda item;

   d. A listing of planned external attendees;

   e. A listing of requested participants/disciplines representative(s) from the Center;

   f. The approximate time that supporting documentation (i.e., the "backgrounder") for the meeting will be sent to the Center (i.e., "x" weeks prior to the meeting, but should be received by the Center at least 2 weeks in advance of the scheduled meeting for Type A meetings and at least 1 month in advance of the scheduled meeting for Type B and Type C meetings); and

3. The Agency concurs that the meeting will serve a useful purpose (i.e., it is not premature or clearly unnecessary). However, requests for a "Type B"

meeting will be honored except in the most unusual circumstances.

IV. CLINICAL HOLDS

A. Procedure: The Center should respond to a sponsor's complete response to a clinical hold within 30 days of the Agency's receipt of the submission of such sponsor response.

B. Performance goal: 90% of such responses are provided within 30 calendar days of the Agency's receipt of the sponsor's response in FY 03 to FY07 (cohort of date of receipt).

V. MAJOR DISPUTE RESOLUTION

A. Procedure: For procedural or scientific matters involving the review of human drug applications and supplements (as defined in PDUFA) that cannot be resolved at the divisional level (including a request for reconsideration by the Division after reviewing any materials that are planned to be forwarded with an appeal to the next level), the response to appeals of decisions will occur within 30 calendar days of the Center's receipt of the written appeal.

B. Performance goal: 90% of such answers are provided within 30 calendar days of the Center's receipt of the written appeal in FY 03 to FY 07.

C. Conditions

1. Sponsors should first try to resolve the procedural or scientific issue at the Division level. If it cannot be resolved at that level, it should be appealed to the Office Director level (with a copy to the Division Director) and then, if necessary, to the Deputy Center Director or Center Director (with a copy to the Office Director).

2. Responses should be either verbal (followed by a written confirmation within 14 calendar days of the verbal notification) or written and should ordinarily be to either deny or grant the appeal.

3. If the decision is to deny the appeal, the response should include reasons for the denial and any actions the sponsor might take in order to persuade the Agency to reverse its decision.

4. In some cases, further data or further input from others might be needed to reach a decision on the appeal. In these cases, the "response" should be the plan for obtaining that information (e.g., requesting further information from the sponsor, scheduling a meeting with the sponsor, scheduling the issue for discussion at the next scheduled available advisory committee).

5. In these cases, once the required information is received by the Agency (including any advice from an advisory committee), the person to whom the appeal was made, again has 30 calendar days

from the receipt of the required information in which to either deny or grant the appeal.

6. Again, if the decision is to deny the appeal, the response should include the reasons for the denial and any actions the sponsor might take in order to persuade the Agency to reverse its decision.

7. N.B. If the Agency decides to present the issue to an advisory committee and there are not 30 days before the next scheduled advisory committee, the issue will be presented at the following scheduled committee meeting in order to allow conformance with advisory committee administrative procedures.

VI. SPECIAL PROTOCOL QUESTION ASSESSMENT AND AGREEMENT

A. Procedure: Upon specific request by a sponsor (including specific questions that the sponsor desires to be answered), the agency will evaluate certain protocols and issues to assess whether the design is adequate to meet scientific and regulatory requirements identified by the sponsor.

1. The sponsor should submit a limited number of specific questions about the protocol design and scientific and regulatory requirements for which the sponsor seeks agreement (e.g., is the dose range in the carcinogenicity study adequate, considering the intended clinical dosage; are the clinical endpoints adequate to support a specific efficacy claim).

2. Within 45 days of Agency receipt of the protocol and specific questions, the Agency will provide a written response to the sponsor that includes a succinct assessment of the protocol and answers to the questions posed by the sponsor. If the agency does not agree that the protocol design, execution plans, and data analyses are adequate to achieve the goals of the sponsor, the reasons for the disagreement will be explained in the response.

3. Protocols that qualify for this program include: carcinogenicity protocols, stability protocols, and Phase 3 protocols for clinical trials that will form the primary basis of an efficacy claim. (For such Phase 3 protocols to qualify for this comprehensive protocol assessment, the sponsor must have had an end of Phase 2/pre-Phase 3 meeting with the review division so that the division is aware of the developmental context in which the protocol is being reviewed and the questions being answered.)

4. N.B. For products that will be using Subpart E or Subpart H development schemes, the Phase 3 protocols mentioned in this paragraph should be construed to mean those protocols for trials that will form the primary basis of an efficacy claim no matter what phase of drug development in which they happen to be conducted.

5. If a protocol is reviewed under the process outlined above and agreement with the Agency is reached on design, execution, and analyses and if the results of the trial conducted under the protocol substantiate the hypothesis of the protocol, the Agency agrees that the data from the protocol can be used as part of the primary basis for approval of the product. The fundamental agreement here is that having agreed to the design, execution, and analyses proposed in protocols reviewed under this process, the Agency will not later alter its perspective on the issues of design, execution, or analyses unless public health concerns unrecognized at the time of protocol assessment under this process are evident.

B. Performance goal: 90% of special protocols assessments and agreement requests completed and returned to sponsor within timeframes (based on cohort year of request) from FY 03 to FY 07.

VII. CONTINOUS MARKETING APPLICATION

To test whether providing early review of selected applications and additional feedback and advice to sponsors during drug development for selected products can further shorten drug development and review times, FDA agrees to conduct the following two pilot programs:

A. Pilot 1 – Discipline Review Letters for Pre-Submitted "Reviewable Units" of NDAs/BLAs

1. This pilot applies to drugs and biologics that have been designated to be Fast Track drugs or biologics, pursuant to section 112 of the FDA Modernization Act (21 U.S.C. 506), have been the subject of an End-of-Phase 2 and/or a Pre-NDA/BLA meeting, and have demonstrated significant promise as a therapeutic advance in clinical trials.

2. For drugs and biologics that meet these criteria, FDA may enter into an agreement with the sponsor to accept pre-submission of one or more "reviewable units"of the application in advance of the submission of the complete NDA/BLA.

3. If following an initial review FDA finds a "reviewable unit" to be substantially complete for review (i.e., after a "filing review" similar to that performed on an NDA/BLA), FDA will initiate a review clock for the complete review of the "reviewable unit" of the NDA/BLA. The review clock would start from the date of receipt of the "reviewable unit."

4. To be considered fileable for review under paragraph 3, a "reviewable unit" must be substantially complete when submitted to FDA. Once a "reviewable unit" is "filed" by FDA, except as provided in paragraph 5 below, only minor information amendments submitted in response to FDA inquiries or requests and routine stability and safety updates will be considered during the review cycle.

5. Major amendments to the "reviewable unit" are strongly discouraged. However, in rare cases, and with prior agreement, FDA may accept and consider for review a major amendment to a "reviewable unit." To accommodate these rare cases, a major

amendment to a "reviewable unit" submitted within the last three months of a 6-month review cycle may, at FDA's discretion, trigger a 3-month extension of the review clock for the "reviewable unit" in question. In no case, however, would a major amendment be accepted for review and the review clock for the "reviewable unit" extended if the extended review clock for the "reviewable unit" exceeded the review clock for the complete NDA/BLA. (See paragraph 10 below).

6. After completion of review of the "reviewable unit" of the NDA/BLA by the appropriate discipline review team, FDA will provide written feedback to the sponsor of the review findings in the form of a discipline review letter (DRL).

7. The DRL will provide feedback on the individual "reviewable unit" from the discipline review team, and not final, definitive decisions relevant to the NDA/BLA.

8. If an application is to be presented to an advisory committee, the final DRL on the "reviewable unit" may be deferred pending completion of the advisory committee meeting and internal review and consideration of the advice received.

9. The following performance goals will apply to review of "reviewable units" of an NDA/BLA for Fast Track drugs and biologics that are submitted in advance of the complete NDA/BLA under this pilot program:

   a. Discipline review team review of a "reviewable unit" for a Fast Track drug or biologic will be completed and a DRL issued within 6 months of the date of the submission for 30% of "reviewable units" submitted in FY04;

   b. Discipline review team review of a "reviewable unit" for a Fast Track drug or biologic will be completed and a DRL issued within 6 months of the date of the submission for 50% of "reviewable units" submitted in FY05;

   c. Discipline review team review of a "reviewable unit" for a Fast Track drug or biologic will be completed and a DRL issued within 6 months of the date of the submission for 70% "reviewable units" submitted in FY06, and

   d. Discipline review team review of a "reviewable unit: for a Fast Track drug or biologic will be completed and a DRL letter issued within 6 months of the date of the submission for 90% of "reviewable units" submitted in FY07.

10. If the complete NDA/BLA is submitted to FDA while a 6-month review clock for a "reviewable unit" is still open, FDA will adhere to the timelines and performance goals for both the "reviewable unit" and the complete NDA/BLA. For example, if a "reviewable unit" is submitted in January and the complete NDA/BLA is submitted in April, the review goal for the "reviewable unit" will be July and the review goal for the complete NDA/BLA will be October.

11. Any resubmission or amendment of a "reviewable unit" submitted by the sponsor in response to an FDA discipline review letter will not be subject to the review timelines and performance goals proposed above. FDA review of such resubmissions and amendments in advance of submission of the complete NDA/BLA will occur only as resources allow.

12. This pilot program is limited to the initial submission of an NDA/BLA and is not applicable to a resubmission in response to an FDA complete response letter following the complete review of an NDA/BLA.

13. Guidance: FDA will develop and issue a joint CDER/CBER guidance on how it intends to implement this pilot program by September 30, 2003. The guidance will describe the principles, processes, and procedures that will be followed during the pilot program. The guidance also will define what subsections of a complete technical section would be considered an acceptable "reviewable unit" for pre-submission and review and how many individual "reviewable units" from one or more technical sections of an NDA/BLA can be pre-submitted and reviewed subject to separate review clocks under this program at any given time. The pilot program will be implemented in FY 2004, after the final guidance is issued and will continue through FY 2007.

B. Pilot 2 – Frequent Scientific Feedback and Interactions During Drug Development

1. This pilot applies to drugs and biologics that have been designated to be Fast Track drugs or biologics pursuant to section 112 of the FDA Modernization Act (21 U.S.C. 508), that are intended to treat serious and/or life-threatening diseases, and that have been the subject of an end-of-phase 1 meeting. The pilot program is limited to one Fast Track product in each CDER and CBER review division over the course of the pilot program.

2. For drugs and biologics that meet these criteria, FDA may enter into an agreement with the sponsor to initiate a formal program of frequent scientific feedback and interactions regarding the drug development program. The feedback and interactions may take the form of regular meetings between the division and the sponsor at appropriate points during the development process, written feedback from the division following review of the sponsor's drug development plan, written feedback from the division following review of important new protocols, and written feedback from the division following review of study summaries or complete study reports submitted by the sponsor.

3. Decisions regarding what study reports would be reviewed as summaries and what study reports would be reviewed as complete study reports under this pilot program would be made in advance, following discussions between the division and the sponsor of the proposed drug development program. In making these decisions, the review division will consider the importance of the study to the drug development program, the nature of the study, and the potential value of limited (i.e., based on summaries) versus more thorough division review (i.e., based on complete study reports).

4. Guidance: FDA will develop and issue a joint CDER/CBER guidance on how it intends to implement this pilot program by September 30, 2003. The guidance will describe the principles, processes, and procedures that will be followed during the pilot program. The pilot program will be implemented in FY 2004, after the final guidance is issued and will continue through FY 2007. The full (unredacted) study report will be provided to the FDA Commissioner and a version of the study report redacted to

remove confidential commercial information or other information exempt from disclosure, will be made available to the public.

C. Evaluation of the Pilot Programs

1. In FY 2004, FDA will contract with an outside expert consultant(s) to evaluate both pilot programs.

2. The consultant(s) will develop an evaluation study design that identifies key questions, data requirements, and a data collection plan, and conduct a comprehensive study of the pilot programs to help assess the value, costs, and impact of these programs to the drug development and review process. A preliminary report will be generated by the consultant by the end of FY06.

VIII. PRE- AND PERI-NDA/BLA RISK MANAGEMENT PLAN ACTIVITIES

a. **Submission and Review of pre-NDA/BLA meeting packages:** A pre-NDA/BLA meeting package may include a summary of relevant safety information and industry questions/discussion points regarding proposed risk management plans and discussion of the need for any post-approval risk management studies. The elements of the proposal may include:

1. assessment of clinical trial limitations and disease epidemiology

2. assessment of risk management tools to be used to address known and potential risks

3. suggestions for phase 4 epidemiology studies, if such studies are warranted

4. proposals for targeted post-approval surveillance (this would include attempts to quantify background rates of risks of concern and thresholds for actions)

The pre-NDA/BLA meeting package will be reviewed and discussed by the review divisions as well as the appropriate safety group in CDER or CBER.

b. **Pre-NDA/BLA meeting with industry:** This meeting may include a discussion of the preliminary risk management plans and proposed observational studies, if warranted, as outlined above. Participants in this meeting will include product safety experts from the respective Center. The intent of these discussions will be for FDA to get a better understanding of the safety issues associated with the particular drug/biologic and the proposed risk management plans, and to provide industry with feedback on these proposals so that they can be included in the NDA/BLA submission. It is the intent of this proposal that such risk management plans and the discussions around them would focus on specific issues of concern, either based on already identified safety issues or reasonable potential focused issues of concern.

c. **Review of NDA/BLA:** The NDA/BLA submitted by industry may include the proposed risk management tools and plans, and protocols for observational studies, based on the discussions that began with the pre-NDA/BLA meeting, as described above, and may be amended as appropriate to further refine the proposal. These amendments

would not normally be considered major amendments. Both the review division and the appropriate safety group will be involved in the review of the application and will try to communicate comments regarding the risk management plan as early in the review process as practicable, in the form of a discipline review letter. Items to be included in the risk management plan to assure FDA of the safety and efficacy of the drug or biologic are to be addressed prior to approval of an application. The risk management plan may contain additional items that can be used to help refine the risks and actions (e.g., background rates and observational studies) and these items may be further defined and completed after approval in accordance with time frames agreed upon at the time of product approval.

d. **Peri-Approval Submission of Observational Study Reports and Periodic Safety Update Reports (PSURs):** For NDA/BLA applications, and supplements containing clinical data, submitted on or after October 1, 2002, FDA may use user fees to review an applicant's implementation of the risk management plan for a period of up to two years post-approval for most products and for a period of up to three years for products that require risk management beyond standard labeling (e.g., a black box or bolded warning, medication guide, restricted distribution). This period is defined for purposes of the user fee goals as the peri-approval period. Issues that arise during implementation of the risk management plan (e.g., whether the plan is effective) will be reported to FDA either in the form of a PSUR or in a periodic or annual report (21 CFR 314.80 and 314.81) (ICH Guidance E2C, Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs) and addressed during the peri-approval period through discussions between the applicant and FDA. PSURs may be submitted and reviewed semi-annually for the first two or three years post approval to allow adequate time for implementation of risk management plans.

   For drugs approved under PDUFA III, FDA may use user fees to independently evaluate product utilization for drugs with important safety concerns, using drug utilization databases, for the first three years post approval. The purpose of such utilization evaluations is to evaluate whether these products are being used in a safe manner and to work pro-actively with companies during the peri-approval period to accomplish this.

e. **Guidance Document Development:** By the end of Fiscal Year 04, CDER and CBER will jointly develop final guidance documents that address good risk assessment, risk management, and pharmacovigilance practices.

IX. INDEPENDENT CONSULTANTS FOR BIOTECHNOLOGY CLINICAL TRIAL PROTOCOLS

A. Engagement of Expert Consultant: During the development period for a biotechnology product, a sponsor may request that FDA engage an independent expert consultant, selected by FDA, to participate in the Agency's review of the protocol for the clinical studies that are expected to serve as the primary basis for a claim.

B. Conditions

1. The product must be a biotechnology product (for example, DNA plasmid products, synthetic peptides of fewer than 40 amino acids, monoclonal antibodies for in vivo use, and recombinant DNA-derived products) that represents a significant advance in the treatment, diagnosis or prevention of a disease or condition, or have the potential to address an unmet medical need;

2. The product may not have been the subject of a previously granted request under this program;

3. The sponsor must submit a written request for the use of an independent consultant, describing the reasons why the consultant should be engaged (e.g., as a result of preliminary discussions with the Agency the sponsor expects substantial disagreement over the proposed protocol); and

4. The request must be designated as a "Request for Appointment of Expert Consultant" and submitted in conjunction with a formal meeting request (for example, during the end-of-Phase II meeting or a Type A, meeting).

C. Recommendations for Consultants: The sponsor may submit a list of recommended consultants for consideration by the Agency. The selected consultant will either be a special government employee, or will be retained by FDA under contract. The consultant's role will be advisory to FDA and FDA will remain responsible for making scientific and regulatory decisions regarding the clinical protocol in question.

D. Denial of Requests: Except in the most unusual circumstances (for example, it is clearly premature) FDA will honor the request and engage the services of an independent consultant, of FDA's choosing, as soon as practicable. If the Agency denies the request, it will provide a written rationale to the requester within 14 days of receipt.

E. Performance Goal Change: Due to the time required to select and screen the consultant for potential conflicts of interest and to allow the consultant sufficient time to review the scientific issues involved, the performance goals for scheduling the formal meeting (see section III) may be extended for an additional sixty (60) days.

F. Evaluation: During FY 2006, FDA will conduct a study to evaluate the costs and benefits of this program for both sponsors and the Agency.

X. FIRST CYCLE REVIEW PERFORMANCE PROPOSAL

A. Notification of Issues Identified during the Filing Review

1. Performance Goal: For original NDA/BLA applications and efficacy supplements, FDA will report substantive deficiencies identified in the initial filing review to the sponsor by letter, telephone conference, facsimile, secure e-mail, or other expedient means.

2. The timeline for such communication will be within 14 calendar days after the 60 day filing date.

3. If no deficiencies were noted, FDA will so notify the sponsor.

4. FDA's filing review represents a preliminary review of the application and is not indicative of deficiencies that may be identified later in the review cycle.

5. FDA will provide the sponsor a notification of deficiencies prior to the goal date for 50% of applications in FY 2003, 70% in FY 2004, and 90% in FY 2005, FY2006, and FY 2007.

B. Good Review Management Principles Guidance: FDA will develop a joint CDER-CBER guidance on Good Review Management Principles (GRMPs), and publish final guidance by the end of FY 2003. The Good Review Management Principles will address, among other elements, the following:

1. The filing review process, including communication of issues identified during filing review that may affect approval of the application.

2. Ongoing communication with the sponsor during the review process (in accordance with 21 CFR 314.102(a)), including emphasis on early communication of easily correctable deficiencies (21 CFR 314.102(b)).

3. Appropriate use of Information Request and Discipline Review letters, as well as other informal methods of communication (phone, fax, e-mail).

4. Anticipating/planning for a potential Advisory Committee meeting.

5. Completing the primary reviews -- allowing time for secondary and tertiary reviews prior to the action goal date.

6. Labeling feedback – planning to provide labeling comments and scheduling time for teleconferences with the sponsor in advance of the action goal date

C. Training: FDA will develop and implement a program for training all review personnel, including current employees as well as future new hires, on the good review management principles.

D. Evaluation: FDA will retain an independent expert consultant to undertake a study to evaluate issues associated with the conduct of first cycle reviews.

1. The study will be designed to assess current performance and changes that occur after the guidance on GRMPs is published. The study will include collection of various types of tracking data regarding actions that occur during the first cycle review, both from an FDA and industry perspective (e.g., IR letters, DR letters, draft labeling comments from FDA to the sponsor, sponsor response to FDA requests for information).

2. The study will also include an assessment of the first cycle review history of all NDAs for NMEs and all BLAs during PDUFA 3. This assessment will include a

more detailed evaluation of the events that occurred during the review process with a focus on identifying best practices by FDA and industry that facilitated the review process.

3. The study will also include an assessment of the effectiveness of the training program implemented by FDA.

4. FDA will develop a statement of work for the study and will provide the public an opportunity to review and comment on the statement of work before the study is implemented. The consultant will prepare annual reports of the findings of the study and a final study report at the end of the 5-year study period. The full (un-redacted) study reports will be provided to the FDA Commissioner and a version of the study reports redacted to remove confidential commercial information or other information exempt from disclosure, will be made available to the public.

5. Development and implementation of the study of first cycle review performance will be a component of the Performance Management Plan conducted out of the Office of the Commissioner (see section X).

6. Administrative oversight of the study will rest in the Office of the Commissioner. The Office of the Commissioner will convene a joint CDER/CBER review panel on a quarterly basis as a mechanism for ongoing assessment of the application of Good Review Management Principles to actions taken on original NDA/BLA applications.

XI. IMPROVING FDA PERFORMANCE MANAGEMENT

A. Performance Fund: The Commissioner will use at least $7 million over five years of PDUFA III funds for initiatives targeted to improve the drug review process.

1. Funds would be made available by the Commissioner to the Centers based both on identified areas of greatest need for process improvements as well as on achievement of previously identified objectives.

2. Funds also could be used by the FDA Commissioner to diagnose why objectives are not being met, or to examine areas of concern.

3. The studies conducted under this initiative would be intended to foster:

   a. Development of programs to improve access to internal and external expertise

   b. Reviewer development programs, particularly as they relate to drug review processes,

   c. Advancing science and use of information management tools

   d. Improving both inter- and intra-Center consistency, efficiency, and effectiveness

e. Improved reporting of management objectives

f. Increased accountability for use of user fee revenues

g. Focused investments on improvements in the process of drug review

h. Improved communication between the FDA and industry

4. In deciding how to spend these funds, the Commissioner would take into consideration how to achieve greater harmonization of capabilities between CDER and CBER.

B. First Two Initiatives: Two specific initiatives will begin early in PDUFA III and supported from performance management initiative funds 1) evaluation of first cycle review performance, and 2) process review and analysis within the two centers.

1. First Cycle Review Performance

   See the First Cycle Review Performance (See section X. for details on this proposed study).

2. Process Review and Analysis
   a. In FY 2003, FDA will contract with an outside consultant to conduct a comprehensive process review and analysis within CDER and CBER. This review will involve a thorough analysis of information utilization, review management, and activity cost.

   b. The review is expected to take from 18-24 months, although its duration will depend on the type and amount of complexity of the issues uncovered during the review.

   c. The outcome of this review will be a thorough documentation of the process, a re-map of the process indicating where efficiencies can be gained, activity-based project accounting, optimal use of review tools, and a suggested path for implementing the recommendations.

   d. FDA would anticipate delivery of a report of the consultant's findings and recommendations in FY 2004-2005. The agency would consider these recommendations in planning any redesign or process reengineering to enhance performance.

3. Further Studies

In subsequent years of PDUFA III, FDA may develop other study plans that will focus on further analysis of program design, performance features and costs, to identify potential avenues for further enhancement. Future studies would be likely to include a comprehensive re-analysis of program costs following the implementation of new PDUFA III review initiatives and the adoption of any process changes following the recommendations of the year 1 and 2 studies.

XII. ELECTRONIC APPLICATIONS AND SUBMISSIONS - GOALS

a. The Agency will centralize the accountability and funding for all PDUFA Information Technology initiatives/activities for CBER, CDER, ORA and OC under the leadership of the FDA CIO. The July 2001 HHS IT 5-year plan states that infrastructure consolidation across the department should be achieved, including standardization. The Agency CIO will be responsible for ensuring that all PDUFA III IT infrastructure and IT investments support the Agency's common IT goals, fit into a common computing environment, and follow good IT management practices.

b. The Agency CIO will chair quarterly briefings on PDUFA IT issues to periodically review and evaluate the progress of IT initiatives against project milestones, discuss alternatives when projects are not progressing, and review proposals for new initiatives. On an annual basis, an assessment will be conducted of progress against PDUFA III IT goals and, established program milestones, including appropriate changes to plans. A documented summary of the assessment will be drafted and forwarded to the Commissioner A version of the study report redacted to remove confidential commercial or security information, or other information exempt from disclosure, will be made available to the public. The project milestones, assessment and changes will be part of the annual PDUFA III IT report.

c. FDA will implement a common solution in CBER, CDER, ORA and OC for the secure exchange of content including secure e-mail, electronic signatures, and secure submission of, and access to application components.

d. FDA will deliver a single point of entry for the receipt and processing of all electronic submissions in a highly secure environment. This will support CBER, CDER, OC and ORA. The system should automate the current electronic submission processes such as checking the content of electronic submissions for completeness and electronically acknowledging submissions.

e. FDA will provide a specification format for the electronic submission of the Common Technical Document (e-CTD), and provide an electronic review system for this new format that will be used by CBER, CDER and ORA reviewers. Implementation should include training to ensure successful deployment. This project will serve as the foundation for automation of other types of electronic submissions. The review software will be made available to the public. .

f. Within the first 12 months, FDA will conduct an objective analysis and develop a plan for consolidation of PDUFA III IT infrastructure and desktop management services activities that will assess and prioritize the consolidation possibilities among CBER, CDER, ORA and OC to achieve technical efficiencies, target potential savings and realize cost efficiencies. Based upon the results of this analysis, to the extent appropriate, establish common IT infrastructure and architecture components according to specific milestones and dates. A documented summary of the analysis will be forwarded to the Commissioner. A version of the study report redacted to remove confidential commercial or security information, or other information exempt from disclosure, will be made available to the public.

g. FDA will implement Capability Maturity Model (CMM) in CBER, CDER, ORA and OC for PDUFA IT infrastructure and investments, and include other industry best practices to ensure that PDUFA III IT products and projects are of high quality and produced with optimal efficiency and cost effectiveness. This includes development of project plans and schedules, goals, estimates of required resources, issues and risks/mitigation plans for each PDUFA III IT initiative.

h. Where common business needs exist, CBER, CDER, ORA and OC will use the same software applications, such as eCTD software, and COTS solutions.

i. Within six months of authorization, a PDUFA III IT 5-year plan will be developed. Progress will be measured against the milestones described in the plan.

XIII. ADDITIONAL PROCEDURES

A. Simplification of Action Letters

To simplify regulatory procedures, CBER and CDER intend to amend their regulations and processes to provide for the issuance of either an "approval" (AP) or a "complete response" (CR) action letter at the completion of a review cycle for a marketing application.

B. Timing of Sponsor Notification of Deficiencies in Applications

To help expedite the development of drug and biologic products, CBER and CDER intend to submit deficiencies to sponsors in the form of an "information request" (IR) letter when each discipline has finished its initial review of its section of the pending application.

XIV. DEFINITIONS AND EXPLANATION OF TERMS

A. The term "review and act on" is understood to mean the issuance of a complete action letter after the complete review of a filed complete application. The action letter, if it is not an approval, will set forth in detail the specific deficiencies and, where appropriate, the actions necessary to place the application in condition for approval.

B. A major amendment to an original application, efficacy supplement, or resubmission of any of these applications, submitted within three months of the goal date, extends the goal date by three months. A major amendment to a manufacturing supplement submitted within two months of the goal date extends the goal date by two months.

C. A resubmitted original application is a complete response to an action letter addressing all identified deficiencies.

D. Class 1 resubmitted applications are applications resubmitted after a

complete response letter (or a not approvable or approvable letter) that include the following items only (or combinations of these items):

1. Final printed labeling
2. Draft labeling
3. Safety updates submitted in the same format, including tabulations, as the original safety submission with new data and changes highlighted (except when large amounts of new information including important new adverse experiences not previously reported with the product are presented in the resubmission)
4. Stability updates to support provisional or final dating periods
5. Commitments to perform Phase 4 studies, including proposals for such studies
6. Assay validation data
7. Final release testing on the last 1-2 lots used to support approval
8. A minor reanalysis of data previously submitted to the application (determined by the agency as fitting the Class 1 category)
9. Other minor clarifying information (determined by the Agency as fitting the Class 1 category)
10. Other specific items may be added later as the Agency gains experience with the scheme and will be communicated via guidance documents to industry.

E. Class 2 resubmissions are resubmissions that include any other items, including any item that would require presentation to an advisory committee.

F. A Type A Meeting is a meeting which is necessary for an otherwise stalled drug development program to proceed (a "critical path" meeting).

G. A Type B Meeting is a 1) pre-IND, 2) end of Phase 1 (for Subpart E or Subpart H or similar products) or end of Phase 2/pre-Phase 3, or 3) a pre-NDA/BLA meeting. Each requestor should usually only request 1 each of these Type B meetings for each potential application (NDA/BLA) (or combination of closely related products, i.e., same active ingredient but different dosage forms being developed concurrently).

H. A Type C Meeting is any other type of meeting.

I. The performance goals and procedures also apply to original applications and supplements for human drugs initially marketed on an

over-the-counter (OTC) basis through an NDA or switched from prescription to OTC status through an NDA or supplement.

Proposed Statutory Language