DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE ACT (PDUFA)

FDA AND STAKEHOLDERS PUBLIC MEETING

Monday, November 14, 2005

8:00 a.m.

Natcher Conference Center
National Institutes of Health
Building 45
Center Drive
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P A R T I C I P A N T S

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Ellen V. Sigal, Ph.D.
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Allen J. Vaida, Pharm.D.
Bill Vaughan
Andrew C. von Eschenbach, M.D.
Susan C. Winckler, R.Ph., Esq.
Janet Woodcock, M.D.
Raymond L. Woosley, M.D., Ph.D.
William A. Zellmer, M.P.H.
Diana Zuckerman, Ph.D.

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Welcome

MS. HENDERSON: Good morning. If you will take your seats we'll get started.

My name is Debbie Henderson. I'm the Director of the Office of Executive Programs at the Center for Drugs. And I'm very pleased to be your moderator for today. I have been told that my primary job is to keep us running on time. And so far, I'm failing miserably.

I want to welcome you to this meeting of FDA and stakeholders public meeting to discuss the Prescription Drug User Fee program, which is now, as all of you, I'm sure, know, heading for its fourth iteration.

In this meeting the Agency is seeking public comment on the current user fee program, including views on what features should be retained, and what we might do to further strengthen and improve the program. And your comments are, of course, very important to us.

I am going to try from here on out to keep

things orderly and on time. I expect we'll have a lot of people wandering in as it was quite difficult to get on campus.

The way our program will go today is we will have opening remarks from Dr. von Eschenbach, and there are a total of six panels for the day; three of them which will occur before lunch. We will still try to get you out to lunch at around 11:50, and I will try to keep everyone's remarks short. I'm speaking particularly to the FDA panel over here.

After lunch, we'll have three additional panels, and then public comment is scheduled to begin at 3:50. And we are scheduled to adjourn at 5:00.

And so, without further ado, I am please to introduce to you our current acting Commissioner of the FDA.

As most of you know, Dr. von Eschenbach is also the 12th director of the National Cancer Institute.

A nationally recognized urologic surgeon,

Dr. von Eschenbach's distinguished career as a key leader in the fight against cancer spans nearly three decades. Prior to accepting the appointment to lead the NCI in January of 2002, Dr. von Eschenbach served as executive vice president and chief academic officer of the University of Texas, M.D. Anderson Cancer Center in Houston, leading a faculty of nearly 1,000 cancer researchers and clinicians. At M.D. Anderson, he also served as vice president for academic affairs, and held the distinguished Roy M. and Phyllis Gough Huffington Clinical Research Distinguished Chair in Urologic Oncology.

Dr. von Eschenbach joined M.D. Anderson as a urologic fellow in 1976, and was invited to join the faculty a year later. Just six years later, in 1983, he was named chairman of the department of urology.

Himself a cancer survivor, Dr. von Eschenbach has had an impact on the fight against cancer that extends far beyond the clinical and academic communities. He is a founding member of

C-Change, and was president-elect of the American Cancer Society at the time that he was appointed to the NCI.

A native of Philadelphia, Dr. von Eschenbach earned a B.S. from St. Joseph's University in Philadelphia in 1963, and his medical degree from Georgetown University School of Medicine in 1967.

Dr. von Eschenbach completed residencies in general surgery and urology at Pennsylvania Hospital in Philadelphia, and then was an instructor in urology at the University of Pennsylvania School of Medicine. He also served as a Lieutenant Commander in the U.S. Navy Medical Corps.

And the FDA feels very honored now to have him now as our Acting Commissioner.

Opening Remarks

COMMISSIONER VON ESCHENBACH: Good morning, and thank you Debbie. I want to begin by thanking you, and also Theresa Mullen for the tremendous effort and hard work in putting this very, very

important meeting together.

And I also really appreciate and thank all of you. I want to thank you on behalf of not just the FDA, but the entire community for your interest and your effort and your commitment in coming here. I recognize how difficult it can be to get on the NIH campus. I just came from another meeting, and not only could they not get on the campus but, in their meeting room, they didn't even have any lights. So you're actually a little further ahead than some of the other groups meeting here this morning at NIH.

But it is not just your effort in coming here, it's the effort that you put in throughout the entire year to work collaboratively and collectively together to help us as a community enhance the health and welfare of the American people.

All of you here today play a very crucial role in helping the FDA fulfill our responsibility and part of that very important public health mission.

Clinical drug review is one of the backbones of FDA. And it's thanks to people who have supported our drug review programs that we are

continuing to bring safe, effective and affordable products to American consumers; and that we continue in that mission to product and advance the health and welfare of Americans and, in fact, people around the entire world.

So it's a privilege to be with you and to join you for this important discussion about how we can better promote scientific innovation, and maximize the efficiency of the medical development process, especially through the reauthorization of the Prescription Drug User Fee Act.

This has never been a more critical goal than it is today. We are in the midst of a virtual revolution in biomedical research. But despite the tremendous progress of recent decades that's led us to this very exciting time, most medical experts still believe that the most exciting and most important innovations are still ahead of us.

And so today we are spending more on

biomedical research and development than ever before. We are discovering and learning and understanding about diseases at their very fundamental genetic, molecular and cellular level. And not only are we understanding the disease processes, but we're understand the person affected by those disease processes.

I have seen this research first-hand here at the NIH. And I, too, join all of the others who are extraordinarily optimistic about the future; so much so that four years ago, at NCI, when I became the director, we set a goal for the cancer program that we would capitalize upon this tremendous progress in biomedical research, and work to eliminate the suffering and death due to cancer, and bring that about by 2015.

But now, having had the privilege to serve as the FDA's Acting Commissioner, I can see that this research being translated into safe and effective new medicines is a critically important step if we're going to have that impact on the patient and the public we are dedicated to serve.

We are seeing opportunities emerge at the FDA as we are overseeing more and more investigational new drugs, and more innovative and

targeted therapies than have ever before been possible or imagined.

PDUFA has, in fact, enabled a lot of this progress to be made available in a timely way to be able to use these opportunities created into interventions that could be delivered to patients in the form of safe and effective medicines; medicines that are approved by the FDA through a process that is more rigorous and more transparent, and more efficient than it has ever been before; and, in large part due to what the opportunities have been provided for by PDUFA.

PDUFA has enabled FDA to obtain the needed resources and adopt modern tools to review human drugs and to make much needed process improvements, such as management reforms and, most importantly, our opportunities in integrating modern information technologies.

But even with all these promising new

treatments that patients have available as a result of improvements that PDUFA has enabled, it is still more important to do more. It is still obvious how much more work yet needs to get done.

And so at the same time that more innovative treatments are reaching patients there are, in fact, fewer new product applications reaching us than at any time in more than a decade. There is now appearing a fundamental disconnect between the tremendous potential that's been for 21st century biomedical technology, and the actual products that are reaching our patients in the future.

There is a disconnect between good ideas in the lab, and even proof-of-concepts, versus the safe and effective treatments that are actually being provided reliably to patients.

And so as we face a real challenge today to bring the promise of the 21st century medical breakthroughs to patients, our challenge for all of us is to find ways to make drugs and other new innovations both safe and affordable, and to

continue to promote high levels of medical innovation that are then delivered to patients.

Our challenge is to continue to adapt our regulatory approaches to accommodate and accelerate the pace of biomedical innovation and the introduction of safe and effective medicines.

I believe that the reauthorization of PDUFA IV is critical and essential to enable a lot of these opportunities to be made possible. The discussion today marks the beginning of a public process to see how we can use new PDUFA legislation to continue to advance biomedical progress.

To meet this challenge effectively we need to do much more than ever before. We need to improve the process for developing safe and effective new medical products by making it as clear, as fast and as cost efficient as possible. And once new treatments have been developed, we need to continue to reduce the cost and improve the quality and reliability of making them--like we have done in other high tech industries--opportunities that are impacting

patients' lives.

We also need to develop means of providing better and timelier information on the risks and benefits of medical treatments after they've been approved, so people can make fully informed treatment decisions. We need to empower doctors and patients to get the most value out of the medical products that are on the market.

All of this is the critical path; the critical path for therapeutic development that we have been talking about at FDA; the path for moving from scientific breakthroughs, backed by NIH and the many research foundations that are creating this opportunity and discovery, to then to actual development of treatments that make the most difference in patients' lives. This encompasses not just the science of developing drugs and devices, but also the know-how for turning an experimental pharmaceutical or biological molecule revealed in a test tube into an effective medical product that can be safely delivered to a patient. This include all the many steps that need to occur

after a new compound has been removed from the laboratory and is placed into and through clinical trials to become a finally finished drug.

One of the major objectives at FDA is to clarify this critical path; simplify it; and help promising medical products navigate through it. To do so, we need to think about all 100 percent of the process, from the pre-clinical phase through the clinical trial period, through the eventual commercialization of the treatment.

How do we do this?

We need superior development science to translate basic discoveries into new and better medical treatments. We need to take the effort required to develop some better tools for developing medical technologies. And we need a knowledge base, built not just on ideas from biomedical research, but on reliable insights into the performance of drugs after they are approved. So we can continue to learn about risks and benefits in the post-market phase.

Enabling these safe and effective new

medical technologies is a fundamental part of FDA's principal mission to protect and advance the public's health. And it is a fundamental part of the goals of PDUFA. At FDA, we are already developing needed information systems and working on collaborations with the National Science Foundation and the NIH, and other research groups, to help provide guidance and support for applied research studies that have the goal of providing the knowledge needed to make the development pathway more clear and more efficient. And we continue to improve our own processes for evaluating new drugs and to advance our commitment for enabling their development through meetings and feedback that we give to scientists every day.

I mentioned the word "collaboration." I mention it because it is a simple fact that we cannot do this alone. Even with all that we are doing, good medical ideas will not necessarily get translated into public health solutions without the collaborative, cooperative integration of all of our efforts; collaborations with our partners from

drug-development companies and health care organizations, to academic institutions and, in fact, other government agencies, along with patient advocacy groups and consumers. All of these are key to making medical innovation a reality.

And collaboration is going to be a key in enabling us to gain the feedback that we need to make sure that PDUFA IV is as forward-looking and as smart as it needs to be in order to advance the development of biomedicine and drug development. I'm confident that we'll bridge the gabs in medical innovation and succeed in providing both safe and affordable products to Americans nationwide.

The opportunities that PDUFA enables are a big part--in fact, perhaps a crucial part--of achieving this promise.

And so today we begin a discussions; a discussion of how we can use this important legislation to move forward; to move forward to seize these opportunities on behalf of Americans. In doing so, we will realize the full public health benefits of the incredible innovations that are

being made in biomedical research. And I trust we will not only fulfill but exceed the wonderful promise that many envisioned when they labeled this "the biomedical century."

I'm convinced that because of the work of FDA, and the work of this community, in helping to move opportunities like PDUFA forward to enhance and enable strategies like critical path, that you will make possible the fulfillment of a commitment and a goal just like the one we made at NCI to eliminate suffering and death due to cancer.

Our opportunities go far beyond just being able to eliminate the suffering and death due to cancer, as incredible as that one initiative may be. What is occurring at FDA, what PDUFA will make possible, and what the critical path will lead us to is not just a transformation of one disease, but a transformation of all diseases; an opportunity to improve the welfare and health of all people and all diseases. And your work and your participation and your cooperation and your contributions today are a critically important step. And I wish you

well in the intensive work of today, and thank the panel and participants for your commitment and contributions. Thank you.

[Applause.]

MS. HENDERSON: Thank you, Dr. von Eschenbach.

Our first panel will include presentations from the FDA. And these individuals will also serve as our listening panel for today. And I'd like to briefly introduce them. I will introduce them all before they speak.

Our first speaker, and second to my left, is Dr. Scott Gottlieb. Scott is the Deputy Commissioner for Medical and Scientific Affairs at the FDA. Immediately to my left is Dr. Janet Woodcock. Janet is the Deputy Commissioner for Operations, and the Chief Operating Officer at FDA.

To the left of Scott is Dr. Steven Galson, who is the Director of the Center for Drug Evaluation and Research. And to his left is Dr. Jesse Goodman, who is Director for our Center for Biologics Evaluation and Research.

We'll start with Dr. Gottlieb.

Panel I - Presentations by FDA

DR. GOTTLIEB: Thank you very much. I just

wanted to start with a brief overview of the legislative history of PDUFA. And then Dr. Woodcock was going to discuss the impact that PDUFA has had on the drug review program at FDA.

[Slide.]

Modern drug regulation, as you all know, started in 1962 with the passage of amendments to the Food, Drug and Cosmetic Act that, really for the first time, put in place a requirement that drugs had to prove that they were effective pre-market. Before that, requirements were just focused on safety. But for the first time, manufacturers and product developers needed to conduct clinical studies to prove the effectiveness of drugs.

[Slide.]

Heading into the 1970s, there began to be some discontent that there was what was being termed a "drug lag" in the United States. Probably

the landmark evaluation of this was done by a University of Chicago economist by the name of Sam Peltzman, who did an economic study showing that drugs were being approved first in Europe and that, in his estimation, his analysis, the delay in the market to new drugs was the deleterious effect of the delay on the public health was outweighing any benefits that were being accrued through that delay.

This kind of analysis continued to build in the '70s, and really reached a peak in the '80s, with renewed emphasis on patient access issues, of getting drugs to patients more quickly, that heightened with the AIDS epidemic in the United States. And all of this discontent and this focus on review times culminated with the passage of the first Prescription Drug User Fee Act in 1992 which, for the first time, gave FDA new resources, based on user fees, for the review process.

[Slide.]

The primary focus of PDUFA I was on decreased review time, so the resources went to

things like medical and scientific reviewers, and it was focused mostly on the pre-market review process, and getting resources for support personnel and field investigators to try to accelerate the pre-market review. The reauthorization in 1998, in PDUFA II, for the first time focused not just on review times, but development times. And so there was an emphasis on cycle times, and trying to build in resources for things that would enable shorter development time; so things like resources for more collaboration between industry and scientists and the FDA that could help improve the quality of applications that the received. So you saw things like that built into the second reauthorization, which I'll elaborate on in a moment.

[Slide.]

And then PDUFA III continued to build on that; put the Agency on a sound financial footing, and also continued to build on pilot programs and other mechanisms aimed at decreasing development times, and addressing issues of multiple-cycle

reviews; issues where applications go through two or three cycles before the Agency is able to reach a final decision on their status, whether to approve them or not.

[Slide.]

One important point I just wanted to back up and make today is that user fees are not unique to the United States, although the United States, I think pioneered their use as a modern approach to funding a regulatory agency, they're now a mainstay in Europe, where the EMEA is funded in large measure by user fees paid by product developers. And the UK's drug authority is funded entirely through user fees.

[Slide.]

I said I'd get back to some of the goals that were built into the PDUFA legislation. Here you see a chart, a breakdown, of the growth in the goals that were incorporated into the PDUFA legislation through a goals letter that was signed with the Secretary of Health and Human Services. So the legislation itself didn't include these

performance goals, but they were negotiated in a side agreement, in a goals letter.

And you can see the growth in the number of commitments aimed at trying to foster increased scientific collaboration between the reviewers and FDA and product developers, all aimed at trying to bring more clarity to the development process and improve the quality of the applications themselves.

[Slide.]

I included this picture--it's a picture, I think, of Steven Galson fixing FDA's mainframe computer.

[Laughter.]

Steven doesn't fix it anymore. This must be when Janet was in charge of the drug center, because Doug Throckmorton's in charge of fixing it now.

But I included this because one of the thing that came with PDUFA III--it actually was incorporated into PDUFA II, as well, but more so in PDUFA III--was a focus on IT as a big part of trying to enable a more streamlined, more clarity

to the development process that FDA. And so for the first time, in PDUFA III you saw commitments built into the goals letter that were specifically aimed at trying to increase the IT infrastructure at FDA< and also increase the use of information technology to try to accelerate the development process, bring more transparency and clarity to it.

[Slide.]

So this is a list of the various goals aimed at electronic applications, specifically, that were incorporated into PDUFA III. And so explicitly in PDUFA III, there was a commitment for a five-year plan to be developed, an IT plan, with specific milestones; and also commitments made to foster the development of electronic applications and electronic submissions to FDA< which has progressed very well under the FDA leadership.

[Slide.]

PDUFA III, more than anything else, put the agency on a sound financial footing, with revenue targets that increased for inflation from 2003, and also adjusters built in to take account

of increasing burdens put on the FDA through the submission of additional applications. And Dr. Woodcock and others are going to talk more about these adjusters that were built into the PDUFA III legislation, how well they've correlated or not correlated with the increasing workload that the Agency's been confronted with, particularly with respect to all that increased collaboration that was built into the successive PDUFA agreements, PDUFA II and PDUFA III, and the increased amount of meetings and other things that the FDA does to help bring clarify to product developers.

[Slide.]

Just to close: why does PDUFA continue to be important? Well, there's no question that the user fees add additional resources to the Agency, and help the Agency deal with the backlog of applications that existed at the time of the original legislation. But even more so than the resources that the PDUFA legislation enabled for the review process itself, PDUFA has enabled a fundamental management transformation inside the

agency that I think sometimes isn't as widely recognized as the resources that it enabled for the review process itself.

And, as Andy discussed, this kind of modernization to the process internally inside FDA is going to be critical, because the evaluation of the new technology that Andy discussed--Dr. Eschenbach discussed--may well be more resource intensive if we're going to make sure that these kinds of new products get to patients efficiently.

Thank you.

MS. HENDERSON: Thank you, Scott.

Dr. Woodcock?

DR. WOODCOCK: Thank you and good morning.

Scott's told you about the background of the program and some of the different legislative phases it's gone through. I'm going to talk about the operation of the Prescription Drug User Fee program, what it really means inside the agency. And then Dr. Galson and Dr. Goodman are going to fill in the details for their specific programs.

[Slide.]

Now, one of the things I think that is of great confusion to the public is: what do these user fees pay for? I'm not going to go through the

fee structure, but as many of you may know, it's divided up. Only a third of the fees come from applications; the rest of them come from levies on the manufacturing plants that are in production, and the products that are out there. And this was simply to spread the load around, and not burden any particular innovator when an application was submitted.

[Slide.]

The Agency doesn't give these fees directly to any entities within the Agency, they're administered in a central way and simply used to supplement the overall budget. And FDA must keep track, however, of how these fees are contributing to the overall process.

In the statute they define something called the "process of review of new human drugs." And that "human drugs" covers drugs and biologics, and that process definition describes what, in

fact, can be paid for by user fees; in other words, activities eligible for support from the fee program. So the Agency collects a centralized amount of money and then that is allocated to support these various activities. It isn't in any manner a fee gets paid in, and then the reviewers know about that. It's simply a support to the activities that go on at the FDA. And I'm going to explain this a little bit more.

Now, what activities are covered? What exactly is paid for or supported by these fees?

[Slide.]

Well, during the investigational phase of product development, in the process of review of new human drugs, the following activities are covered. And isn't a totally exhaustive list, but it's most of the important activities.

First of all, the FDA has to decided, when a compound is ready to go into people, whether or not the safety data that has been generated about the new compound, whether it's a gene therapy or a new molecular entity or a vaccine, or whatever it

is, and whether the safeguards that have been put in place are adequate to put that compound into the first person, and to initiate human testing.

So this is obviously an extremely important function, and this is supported by user fees.

Secondly, as the investigational progresses, and more and more people are exposed at higher doses or whatever, the FDA sets standards for the safety evaluation at each stage of this development. So the FDA reviewers must specify what safety tests are going to be done on the patients--all the patients; how long they'll be followed, and so forth. And in many areas, as probably Jesse will tell you, this is extremely tricky; for example, in some of the newer areas such as gene therapy, how long should the people be followed, how should they be monitored? But in any new intervention, a lot of attention has to be paid to this.

[Slide.]

Thirdly, the FDA has to set the

requirements for how the dose is arrived at. This is a very important aspect of development. It's important for safety and also for utility or usefulness of a drug or biological.

And, finally, the FDA has to set standards for how the trials are conducted; what the design of the trial is. What are the endpoints for any given indication? In other words, what defines success? How long do people have to be exposed? What do you measure about the people?

And all these activities, my point is, are covered by the user fee program. And you can see they're very essential to making sure that products are properly evaluated, and subjects are kept safe.

This isn't all.

[Slide.]

As Scott alluded to, during the investigational phase, the FDA scientists must interact and advise developers on their trials; for their specific trial; not the standards, but that specific set of trials they're doing; what kind of safety monitoring they're going to do in that

specific time. Trial endpoints should be agreed to with the FDA.

In the past, during the drug lag times, one of the problems was that many volunteer subjects, patients and others, were exposed to trials that ultimately turned out not to be useful. Either the FDA would not accept them; they were poorly designed; or they had the wrong endpoints. This is basically not ethical. And therefore it is very important there be interaction between developers and the regulatory agencies to make sure the correct trials are done; trials that will yield the information that is desired, and that won't unnecessarily expose human subjects.

[Slide.]

Another important function that's covered by user fees is the need for the FDA to continually monitor the development of adverse event; side effects or other adverse events that occur in the clinical trials. And the FDA will place clinical holds on trials if some risk signal occurs in the trials, or require modification; for example, ask a

firm not to study higher doses, continue accruing more patients at lower doses and so forth, to ensure maximal safety of the subjects.

This is quite different than the role of the IRB--just for your information. The FDA has the scientific expertise in development of those specific products, and therefore has a lot of wide-spanning knowledge about the development programs; what can happen, and what to do. This is really synergistic with the IRB function. People in the IRB are looking for the ethical protection of the subjects: make sure that informed consent is accurate and that people are safe. But these are complementary functions.

[Slide.]

In addition, the FDA oversees clinical research through its bioresearch monitoring program. The FDA inspects IRBs that oversee trials of regulated products, and we also set standards and policy for these IRBs in this realm.

We also inspect the conduct of the trials of regulated products, and we set standards for how

those trials be conducted. And that's called the "good clinical practice standards." Those are internationally harmonized standards for trial conduct, record keeping and so on. This also is covered by user fees. This obviously is a very important activity.

[Slide.]

Now when an application--a marketing application--is submitted to the FDA, there's a whole other set of activities that are covered by user fees. The FDA must review how the product is manufactured, and what controls are put on the manufacturing, and what testing is done on the product to make sure that it can be manufactured reliably at high quality.

The FDA also sends people out to inspect the manufacturing facility. And the FDA also looks at the packaging, or how the product is going to be shipped, and make sure it's stable and all sorts of things there.

The reviewers must look at animal toxicology that probably will elucidate things that

you won't have found in the clinical trials; for example reproductive toxicity. We don't really study pregnant women usually in trials, and therefore we're extrapolating our findings about reproductive toxicity from animal studies.

Same with carcinogenicity: those are long-term studies that are done in animals to make sure that products are not going to be causing cancer; something you wouldn't find in the clinical trial program usually.

[Slide.]

What gets most attention during this phase is the FDA reviewers have to review the clinical data, both all the safety data. In addition, the FDA has to review the product for mix-ups; to look at the name of the product and other aspects of the product that could lead to confusion and medical errors, and potential deaths when the product was out in the market. And the efficacy data.

And, finally, the FDA reviewers look at and negotiate with the company on what is said in the drug label, which is the standard for what is

truthful about the drug.

[Slide.]

In addition, around an approval a number of other activities happen. These are also covered by use fees: holding public advisory committee meetings; evaluating risk-management plans. If there's an identified risk of a product, then it's very desirable to, instead of just waiting for something bad to happen, to have a plan in place to try and manage that risk. Agreement on Phase IV commitments, and then we have to review those Phase IV studies and the results. These are all covered by user fees.

[Slide.]

Now, that's the scope of the activities that are covered. And there are probably others that I haven't mentioned. There's certain product testing that goes on. There's other things that happen.

Now, we've heard from our stakeholders over the years many, many times: there is wide support for FDA carrying out each of these

activities. That is not to say there are always some people who think FDA shouldn't do these things. But the vast number of people believe FDA should carry out each one of these activities and, in fact, most of our stakeholders call for us to do more in each one of these areas, depending on what they're concerned about and what they're interested in. They want us to do more drug safety. They want to improve the development process for unmet medical needs--as you heard from Dr. von Eschenbach. They want more oversight of clinical trials of medical products and so forth.

But each of these activities require adequate scientific staff, with appropriate IT and support staff.

[Slide.]

Now, what the user fee program did, by supporting these activities, is enable the FDA to increase the staffing and the bioinformatics, the information technology systems, for these processes. The blue bars here, starting in 1992 on your left, and going through 2004, the blue bars

show the total number of people against these activities that I just talked to you about. And you can see there's been an increase from about maybe 1,300 in 1992, to a little over 2,500 now.

So, there has been significant increase in the number of scientific staff that FDA has been able to put against these activities. And there has been a concomitant increase in many of these activities, as you'll see later.

The pale yellow bars are the appropriated FTEs; in other words, the full-time-equivalents, or the number of people FDA has available from appropriate dollars, to oversee these activities, conduct these activities. And you can see that that number has gone down from 1992 to 2004.

So today, FDA has somewhat fewer people to perform these activities that are funded by appropriated dollars than we did in '92.

The maroon bars show the growth in people that was provided by user fees starting in 1993. And you can see in 2004, the Agency had more staff provided by user fees against these activities than

we had staff provided by appropriations.

By putting these two bars together, though, and getting the blue bar, we do have staff that cover each one of the activities I went over. However I know the programs by no means feel they have excess capacity.

[Slide.]

Now, what happened with this increase is fairly well known. With more staff and also better managed process, FDA was able to reduce the review times. And overall, priority in the yellow bars here, that's really against unmet medical needs, basically. And then the standard applications are in the gray bars, where there are alternatives out there already. You can see that the time for review of each of those came down during the course of the program. And so there is a significant increase in access to new drugs and biologics. And you're going to hear more about that, I think, from the folks here, the other folks.

But more staff and a better managed process have also resulted in better scrutiny by

the agency of the applications, and better articulation of the standards. And this is very important.

Just for example, CDER issued a reviewer guidance on how to do a safety review about a year ago; how to go through the safety review, and how to prepare a report on the safety review. This is an 85-page document.

The current modern safety review is an extremely complex activity. And this is not only for the reviewers, but also explains in a way to the companies all the bases that need to be covered. The reviewers are not only asked to say what's in the application about safety, but what is missing; what hasn't been studied.

Review templates by various centers have been developed. A huge number of guidances have been issued by FDA that explain the standards for many important topis. And the review function has been progressively organized and reorganized to really hone it, to make it efficient.

[Slide.]

PDUFA has also provided value for industry. Because of the decrease in review time, there are big savings for the companies because of

the shortened time to get on the market. And the meetings that are held during the user fee program to provide consultation from the FDA are highly valued by companies, as a recent MIT study showed.

[Slide.]

What are the current challenges for this program, however?

Number one is workload. As you'll hear probably from Dr. Galson and Dr. Goodman, one of the issues is the way the fee adjusters are structured really had to do with the number of applications coming in. But once the meetings program was established as part of the user fee program, the desire for meetings with the FDA in consultation has risen sharply. And this is not accounted for; this workload is not accounted for in the fee adjusters.

There are additional challenges for the FDA which we could get into in the discussion, if

we wish. One, the IT infrastructure and bioinformatics support is still very challenging. Many people have raised issues about direct consumer advertising regulation; the oversight of clinical trials. Again, that is one of the activities covered under the PDUFA program. Again, as a clinical trial conduct changes, it's becoming very challenging. And then preparing for the impact of the new science, as new science starts to really come into the Agency as very innovative products are developed, these tend to be more labor intensive and also raise challenges.

So that's an overview, I think, of the program as it stands. And I thank you very much.

Oh, one more.

[Slide.]

The fees--now the total fee, similar to the user fee FTEs, currently user fees in 2004 began outpacing the appropriated dollars for the program. So it is not a majority user fee funded program.

Thanks.

MS. HENDERSON: Thank you, Dr. Woodcock.

And now, from the perspective of the Center for Drugs, Dr. Steven Galson.

DR. GALSON: Thank you very much, Debbie. And I'm happy to be here to talk to all of you. I'll try to make up for a little bit of our being behind schedule, and zip through these.

I'm going to talk about five issues.

[Slide.]

The first is a little bit more detail about the submission trends, and the data for the work coming in; the impact of that and PDUFA on the number of meetings that we have with sponsor companies; the result of all this being approval of more new lifesaving drugs; what we've been able to do in terms of increasing the expertise of our staff; and then a little bit on the very, very contentious issue of the connection of PDUFA with the safety of drugs on the market that I know you've all heard a lot about.

There are a lot of different ways to measure how much work is coming into the Agency and

into the Drug Center. And these are three graphs that cover NDAs, efficacy supplements and manufacturing supplements. And you can see, in general--you're not meant to look at the fine points here--but over the entire period of PDUFA, there's been a gradual increase in the submission of these documents for review by our staff, with ups and downs. It's leveled off pretty much in PDUFA III, but you can see the large trend.

But that doesn't really tell the full story, particularly bout what's happened in PDUFA III. Dr. Woodcock touched on this already: and that is the fact that we've gotten a huge increase in the request for meetings, particularly under PDUFA III. You can see we're up almost to--we actually are up to 2,000 meetings a year in FY 2005. That's a lot of meetings.

And, of course, that doesn't tell the full story either, because with each meeting that we hold with a sponsor company, our staff has to have at least one, or probably two, preparatory meetings to figure out what the approach is going to be.

And then after the meeting takes place, there have to be a series of meetings among the staff to figure out the actions that are going to be taken as a result of the meeting.

So this is really a huge uncompensated area of growth in work under PDUFA; being very positive for public health and for review and access to new products, but putting huge pressure on our staff and managers.

[Slide.]

Another way to look at this is the special protocol assessments that we do associated with the early phase of drug development; again, very positive for getting new products on the market, but creating a huge workload for our staff. We provide an assessment in writing within 45 days of getting these special protocol assessments into the Agency. And you can see the large growth in those, again putting pressure on the staff to do more. And these cover clinical pharm tox and all sorts of other areas, as well: stability.

[Slide.]

The result of all this, again on the positive side, is that the cycle time, the number of times applications go back and forth between the

agencies and the companies, has gradually reduced throughout the duration of PDUFA. And this was, of course, one of the goals. We're down to, you can see, in FY'04 really close to one to a cycle to NDA approval. And this is, of course, a huge improvement over two.

And the result of all this is that lots of new products have come to market; very, very important for patients.

[Slide.]

There were 226 priority drugs that represent significant therapeutic advancements, including--and this is not a comprehensive list at all--59 cancer -related products, 144 products to treat infections of all kinds, 63 specifically for HIV and hepatitis viruses, and 73 cardiovascular drugs. So these really cover the gamut of the real pressing public health needs of American patients.

[Slide.]

And, again, just by way of example, not a comprehensive list at all--and I don't mean to insult any area that's being left out of this--touching on a few key cancer-related approvals, one from a few years ago: Gleevec, and then more recently for leukemia and lymphoma

Arranon; drugs to respond to the counterterrorism threat, to treat people who have been exposed to radiation; Alzheimer's disease, a very, very difficult therapeutic area; again focusing on HIV in children; and a very, very important advance, Reyataz IV, enabling patients to take one-daily HIV treatment, instead of this huge cocktail of pills that have to be taken across the day in multiple different combinations; drugs to treat chronic problems like alcoholism; and, again, fairly recently, Bidil was approved to treat a specific sub-population in Black Americans who are particularly at risk for certain kinds of heart failure.

So many of these represent important incremental advances in therapies, very important

to patients and physicians who spend their lives trying to improve outcomes.

[Slide.]

The result of the program has as well been to allow us to dramatically increase our scientific expertise. And this again doesn't cover all of the areas of our scientific expertise, but just a few. And I'll point to some of these numbers.

We've increased physicians by 40 percent; pharmacists by 47; general health sciences by 56 percent; toxicologists by 50 percent. And the pie chart covers some of the top five medical specialties. You can see: internal medicine, pediatrics, neurology have all grown substantially. And that's very, very important. That gives these applications the opportunity to be seen by more people, more people with a broad expertise across the board in medicine; very, very important to us doing a better job.

[Slide.]

There has been a lot of attention to safety investments, and safety improvements, and

concern about the safety of our products. Some of this attention has caused us to go back and look very carefully at how much of our resources are spent on safety. And we've had to repeat this message over and over again: that safety is an important achievement and an important area of attention across the board in the Center for Drug Evaluation and Research and, I know, CBER as well. It's not just focused in one or even a couple offices. Across the board in CDER, we spend 50 percent of all of our resources on drug safety. And this touches every single one of our offices.

There's a lot of additional work, attention, investment, and research, and procedure that has to happen in the drug safety area. But we have managed to make improvements and increases in investment in drug safety under the PDUFA program. Particularly with the last round of PDUFA, we're able to spend some of the user fee funds on post-marketing surveillance. We hope to see that continue and maybe be expanded.

[Slide.]

We've been working on reorganizations of the Center for Drug Evaluation and Research to focus more attention and staff on drug safety

areas, both process of reviewing the drugs and developing policies, with appropriated funding earmarks, and increased focus on PDUFA IV as I've talked about. And we've got $10 million new dollars in the FY'06 budget that we hope will actually result in an increase as the budget process rolls up to a finish, which is going to be very, very important.

So these changes have resulted in continued improvements in both pre- and post-market safety in products.

[Slide.]

But to really make important strides in drug safety--and we have to focus on this over and over again--we have to continue to keep our eyes on scientific investments; investments in ways of reviewing drugs, in ways of looking at data, and creating data that allows us to better predict the safety of products, and better identify safety

problems that drugs run into after approval. Without that scientific improvement, it's going to be tough to really make important large-scale increases in the safety of products.

There has been some attention among academic and outside researchers on the effect of PDUFA on drug safety. You're going to hear about those in more detail today from some of the authors. Researchers both at Tufts and MIT have shown that there hasn't been any difference in drug withdrawals across the PDUFA program as compared to the pre-PDUFA area.

[Slide.]

So, in summary, we feel that the program has dramatically contributed to public health and improved drug review; the expertise of CDER staff; the processes in CDER have dramatically improved over the course of the program. We've made some advances in safety, but we need a lot more. And I think we can all agree with that.

And, lastly, again, we haven't seen any evidence of a relationship between these advances

in speed and adverse impact on safety of the products that are approved.

Thanks.

MS. HENDERSON: Thank you, Steven.

And last, but certainly not least, from the Center for Biologics, Dr. Jesse Goodman.

DR. GOODMAN: Good morning. You're going to hear some recurrent Themes, and I'll try to zip through this quickly.

[Slide.]

But let me just say, as it says at the bottom here, when you look at the vision of our center, which is to improve public and individual health, including, where possible, globally; and truly not just assure products are safe and effective, but facilitate their development and access to them; and then strengthen us in terms of our expertise and abilities, PDUFA has provided essential support in those areas. And I think Janet's breakdown of the support that PDUFA has provided FDA is very illustrative.

I should mention that this is a process

that has global impact, not just U.S. impact. It's increasingly an international industry and, for example, I just came back from a WHO meeting where, if you look at some of the promise of some of the products developed here, vaccines for Rhoda virus, vaccines for haemophilus, which have pretty much eliminated that form of meningitis in this country, the potential benefits of those all over the world is just incredible.

[Slide.]

This is just a little bit about our performance under PDUFA. And as Steve and Janet have said, it's not just the funds--and Scott also mentioned--it's also how we look at and manage the process, and putting energy into the effectiveness and efficiency of what we do.

And I think this shows you, going from '93 there on the left, to '97 here, the timeliness of meeting first actions within goal on PDUFA I, then PDUFA II, and most recently with PDUFA III. And you can see we've moved from an organization where there were these delays and lags, to one that is

highly efficient in meeting what, for us, were very large and complex applications, I think is an efficient review process.

[Slide.]

Steven mentioned the meetings. These are extremely labor intensive. We find them very valuable, not just for companies, but also for our people to have an interactive, science-based process which leans much more to what I talk about as problem solving rather than just problem finding, which is what happens when a process is completely iterative.

[Slide.]

And here again you can see the improvements over time, PDUFA II, and the very high level of performance in meeting various meeting actions in PDUFA III.

[Slide.]

As you saw with the Center for Drugs, this has translated, I think, into a very development process. It doesn't mean there aren't challenges for development that remain for both the developers

and the FDA, but I think you can see here the number of cycles has dramatically gone down for both standard and priority BLAs. And I think that's a very important accomplishment that indicates that a lot of this communication is working.

And I have to say that I find usually when problems occur they're about communication. So I think communication is a very good investment.

[Slide.]

You heard a bit about the number of meetings, and we see similar things. In addition to these PDUFA meetings and formal meetings, we also have a tremendous number of informal meetings, phone calls, that both result from those meetings, or take the place of them. And, again, I think that this is a form of communication that, as Steve said, it's not just these formal PDUFA meetings that we track that have grown, but all the communication and planning that occur around them. And I think everybody agrees this is valuable, but labor intensive.

[Slide.]

What are some of the results on this health level? This is just an example again, as

Steve provided, of some of the recent important approvals. The first accelerated approval based on probably surrogate markers of a vaccine this year, bringing another influenza virus vaccine manufacturer into the United States; a new technology of conjugate meningococcal vaccine; new combination products for boosters in immunization in the country; a number of new immunoglobulin, so important in treating immunodeficient patients, whether congenital or acquired; products for Rhesus immunization; products for preparing us for bioterrorism, such as vaccinia immune globulin, very high profile products.

In addition, for many of our products, their use is broad, and they're assessed in different settings, and there are some important efficacy supplements for hepatitis A vaccines and coagulation factors.

[Slide.]

So, again, to summarize, PDUFA has been an important factor in supporting an expert and also efficiently managed review process at FDA, including CBER.

I think an extremely important feature is the intensive interactions with sponsors during

product development. And I would also say the impact of this goes beyond the meetings. There's a cultural impact, I think, for both manufacturers, investigators and academia and the FDA.

I'd also like to say that for some the new technologies, as Janet mentioned and Dr. von Eschenbach mentioned, these interactions are particularly important. They enable us to share information with industry that can help them in the development process, and they also enable industry to keep us up to date.

They also point out areas where there are needs for guidance, which again can be very important when you're dealing with things like cell and gene therapy, where you're sort of blazing new pathways, but can also be quite important for

existing products as they evolve.

And we think the result, in part, is earlier access to safe, effective and innovative products. And these are products, such as vaccines, and blood products, in our center, that are essential to both medical care and our public health system, and to our country's preparedness.

So, that's our summary of performance, and the role of PDUFA in our center.

So we'll look very much forward to your input today and in the coming months.

Thank you.

MS. HENDERSON: Thank you, Jesse. And thanks to our first panel.

I'm going to ask our second panel to come forward an join me at the table to my right. That would be the panel of academic research groups, which includes Doctors Kaitin, Woosley, Berndt and Tilson.

And while they're coming forward, I will introduce the first of the speakers on that panel, who is Dr. Ken Kaitin.

Dr. Kaitin is the Director of the Tufts Center for the Study of Drug Development, an academic drug policy research group providing

strategic information to help drug developers, regulators and policy makers improve the quality and efficiency of the drug-development process. Dr. Kaitin is also associate professor of medicine at Tufts University School of Medicine.

And so, without further ado, will let Dr. Kaitin get started.

Panel II - Presentation by Academic Research Group

DR. KAITIN: Good morning. Welcome. It's a pleasure to be here, and I appreciate the opportunity to participate in this hearing.

As you just heard, I am director of the Tufts Center for the Study of Drug Development. And for 30 years we have collected and analyzed drug development data to report on the time, cost and risk to bring new products to market.

What I will talk about here is a series of analyses that we began in 1985 to look at new drug approvals by the FDA, and trends in times and

marketing of those products. I believe that these three-year trends give us a good example, or good illustration, of changes that have occurred in the United States as a result of the Prescription Drug User Fee Act.

My talk is going to be divided up into four themes.

[Slide.]

The first theme is something that we've already heard about to some degree, and certainly many people are aware of. There are conferences and other workshops that are devoted to the issue of productivity in the industry.

Over the years we have looked at the numbers of products that have been approved. Again, these are in three-year intervals.

[Slide.]

If we look at the number of products approved, there was a big jump in 1996 to '98, as the FDA was clearing out the backlog as a result of the mandate of the Prescription Drug User Fee Act. And then that number declined.

Now, what we had looked at and seen over the course of leading up to this last three-year interval, is that although there was--I don't know

if you can see this--there was a drop in standard drug approvals, the number of priority approvals remained remarkably consistent over the past decade or so. However, in the most recent time period that we've looked at, we've seen a drop-off also in priority drug approvals, and that drop-off represents a drop of 34 percent.

So the decline in productivity affects not just standard approved products but also priority approved products.

Now, why is there this drop-off in productivity?

[Slide.]

One of the main reasons is the increasing time cost and, of course, the riskiness of new drug development times and approval times over two decades, again starting in this first time period, '84 to '86, and looking at the most recent time period, we've seen the well-described reduction in

FDA approval times--these are not review times, but approval times--there was a slight increase, but that's an insignificant increase, in the 2002 to '04 period.

However if we look at clinical development times over that same time period--and this refers to the time from IND filing to NDA submission--we see, after an initial drop-off after the '93 to '99 period, down to 6.4 and then 5.8 years, we've now seen a continuation of the trend that we were seeing prior to PDUFA of seven years to get these products through the clinical testing phase. That's an increase of 21 percent; certainly supporting the notion that it's getting more difficult, and consequently more expensive and difficult to get products through the clinical development process.

Very significantly, this affects not just standard drugs but also priority drug approvals. Again, prior to PDUFA we saw this steady increase in the amount of time that priority drugs took to get through the clinical development process. We

did see a drop-off post-PDUFA, but now we're almost up to the level of the pre-PDUFA period in the amount of time it takes to get priority drug approvals, the most important drug approvals, through the clinical development process.

This increase from 5.6 to 8.1 years represents a 45 percent increase in clinical development time. And, of course, if you add the increase in overall priority approval times of 33 percent, you end up with a considerably long period of time to get these products through the development process than we've seen in past years. And this is, of course, a cause of concern.

[Slide.]

And it's not just the priority versus standard. If we look across different therapeutic categories, we can see that, in fact, the trend is fairly consistent across those categories.

Just to work you quickly through this slide, this is seven therapeutic categories, across the bottom: anesthetic/analgesic, endocrine, anti-infective, neuropharmacologic, cardiovascular,

respiratory, and anti-neoplastic. And this is the clinical development time for the '96 to '98 time period. And then we can put the '99 to 2001. But if now we look at the most recent time period, in five of the seven therapeutic categories there, we see the longest clinical development time in the nine-year period for those categories; most significantly, 11.1 years in the neuropharmacologic area. Coincidentally, it was just about a month ago or three weeks ago that the FDA said that they were going to look into longer clinical development times to get more efficacy and safety data on neuropharmacologic compounds. In fact, the advisory committee that reviewed this voted unanimously not to extend the length of the clinical development times, or clinical trial size, for neuropharmacologics. And I would say this is an example of the process working the way it should.

[Slide.]

Drug Safety. Dr. Galson just discussed that. We are one of the groups that have been

looking at this since we first looked at the drug-lag issue in the 1970s. At that time, the issue was: are we slower but safer? Now the question is: are we faster but less safe?

[Slide.]

And confirming some of the data that the FDA itself has put out, if we look at the total number of approvals going back from 1980 through 2004, these are the total number of approvals over those years. If we look at the withdrawals of products for safety reasons based on the year that the product was approved, we see no consistent trend, despite the increase of six numbers of products that were withdrawn from the 1997 time period. The fact is, there were very few before that, very few in the later years, despite the fact that some of these products may still come off the market, the fact of the matter is: there is no consistent trend in the products that have been taken off the market for safety reasons.

[Slide.]

And, in fact, if we look at the pre-PDUFA

period of 1981 to 1992, and then the post-PDUFA period of 1993 to 2004, we see the total safety withdrawals of eight and 11, which is 2.8 percent for the first period, pre-PDUFA, and 3.1 percent--a slight increase; these are exactly the same numbers that the FDA put out in their safety report recently--this is an insignificant trend, again reflecting the fact that the overall percentage of products taken off the market for safety has not gone up post-PDUFA.

Significantly, much of the debate is focused on whether there is a relationship between speed and likelihood of a product being withdrawn for safety reasons. Dr. Galson talked about this.

[Slide.]

If we look across therapeutic categories, we look at all approvals and then those that have been taken off the market, we see in some therapeutic areas--respiratory, cardiovascular--the time to approve the compounds that were withdrawn was faster than those that were not; but in other therapeutic categories, it's the same or even

longer to review the compounds that were eventually taken off the market for safety reasons.

The bottom line is that there is no relationships--no relationship whatsoever--in the time to approval and the likelihood of a product being withdrawn for safety reasons.

[Slide.]

The final theme I wanted to discuss is the attractiveness of the U.S. market. I think starting in the early 1990s with the Prescription Drug User Fee Act, as well as many other issues and features of the United States market, the United States market is a very attractive market for manufacturers to bring their products to market first in this country.

[Slide.]

In fact, in the most recent analysis, 55 percent of the new drug approvals in the United States were first marketed in the United States. And you can see the numbers for the prior marketing of those compounds.

[Slide.]

To get a better sense of how this has changed as a result of the Prescription Drug User Fee Act, in the top line here--the blue line--this

is more than one year of foreign marketing. That was already declining somewhat, but I believe that PDUFA hastened that decline rapidly. And although there's been a slight increases, that's a very small increase.

The fact of the matter is: the U.S. as a first market for new products has gone up consistently for this time period, despite the small change there, and now is at 55 percent of new product approvals marketed first in the United States.

So, in conclusion: there is a decline in NME output, and that has declined over the PDUFA era, and that includes not just standard but also priority compounds. There is an increase in clinical times, and that has become somewhat of concern because it's offsetting some of the benefits that we have seen in terms of the reduction in approval time to get these products

through the FDA.

Despite this slight rise in percentage of products withdrawn for safety, there is no clear evidence that there is a correlation between speed of approval and the likelihood of a safety withdrawal. So the U.S. remains an attractive market for first launch of prescription drugs.

So moving forward, I echo what was stated by Dr. von Eschenbach and others from the FDA: the FDA needs to continue working through the critical path to identify better mechanisms for assessing safety and efficacy, moving through the clinical development process; and also the FDA should be looking to identify and address regulation-related causes of lengthening clinical development times.

And, in terms of drug safety--again echoing something stated by Dr. Galson--the FDA should be looking for better systems of identifying safety problems early on, before products move through the clinical development process, but also better systems for identifying and taking action on products that have significant adverse events, once

those products are on the market.

Thank you.

MS. HENDERSON: Thank you, Dr. Kaitin, very much.

Our next speaker, well known to this audience, is Dr. Ray Woosley. Dr. Woosley is currently the president and CEO of the Critical Path Institute, also known as C-Path, which is a nonprofit corporation formed by the FDA, SRI International, and the University of Arizona to accelerate the development of safe and innovative medicines.

Since 1999 he has also directed one of seven federally-funded centers of education and research on therapeutics, also known as the CERTs.

Dr. Woosley?

DR. WOOSLEY: Thank you. Thank you for the invitation to say a few words about PDUFA and how important it is. As you can tell, I'm a devotee, a convert, to the critical path. I've been drinking from that lemonade that Janet's been serving, and have a great deal of concern about the drug

development process.

In the next few minutes, I'm going to quickly go through some slides, many of which you've already seen, to talk about the impact of PDUFA; talk about how it relates to the Critical Path Initiative; the purpose of the Critical Path Institute that we've created, but only as a model, not as a solution to the problem. I don't think we can take that on--but as a model for new relationships; and then a proposal for a PDUFA initiative.

As you see, the review times have come down.

[Slide.]

I'm going to quickly go through this slides. You might say it was already heading down, but it clearly has had an impact, and there's no doubt about that.

[Slide.]

There has been a product approval increase transiently, as you've seen. And Ken has more recent data to reinforce that point. Also, the

submissions increased transiently, but they've gone down again.

[Slide.]

At a time when we as a nation--and I think everybody here knows this diagram from the Critical Path Initiative showing the investment in U.S. pharmaceutical R&D increasing 250 percent, and the NIH budget doubling in recent years, so we've made a tremendous increased investment in science, but the number of new products, new drug applications during that time as decreased. New biological applications have decreased.

So PDUFA has done some very good things. It's given the Agency the resources it needed to get rid of the backlog. But I think it's also unmasked another problem that exists in pharmaceutical or medical problem development.

[Slide.]

Part of that is in the success rate. It still remains a very high risk business, with these data in '04 showing 11 percent. That may be a decline from 19 percent success rates 10 years

before that. So we still have either a declining, or at best, a very low success rate in a very high-risk business. And the question is: what is happening to the incentives? What's happening to the return on investment of the over $60 billion we spend on pharmaceutical R&D each year?

[Slide.]

Again, the Critical Path Initiative called this problem to my attention, and I think all of our attention, in the fact that pre-clinical development and clinical development these delays are the biggest part of the problem. And I think Ken's numbers that he showed today reinforce the increasing development time as the major disincentive to investment in new medical product development.

[Slide.]

The response to the Critical Path Initiative has, I think, been overwhelmingly positive. There have been very few negative responses. I think everybody wants new medicines. They want them quickly. They want them to be safe.

In the pharmaceutical industry, several companies have created their own Critical Path Initiative task forces to work and develop their own internal processes for improving the processes.

[Slide.]

The NIH collaborations have grown. The FDA has collaborations with NCI, and Human Genome Research Institute, to address the Critical Path Initiative. And academic, as you've heard--well, I also mentioned the Critical Path Institute--we're really not part of academia. We're a nonprofit outside of the University, but partnering with several universities, including our founding partner, the University of Arizona.

But within academia, without even funding available, units have been created at UCSF, the Center for Drug Development Science, that Carl Pack leave, and JETS, have begun to work on the Critical Path Initiative at MIT, I think you'll hear later, the Center for Biomedical Innovation was created; at Indian, ISIS; the ECG Warehouse, at Duke. And now we've just heard last week about 11

universities that are coming together to address the manufacturing challenges that are identified in the Critical Path Initiative.

So I hope I can say with confidence that everybody believes that this is something who's time has come.

[Slide.]

We certainly looked at that and created a nonprofit, publicly funded. We have $10 million from the State of Arizona, and the community, to create neutral ground where scientists from the FDA, academia and pharmaceutical industry can work together to accelerate the development of safe medical products.

Well, you may say: well, that's happening already. I think that's good. And we've heard about the collaborations.

We believe that this "neutral ground" concept is important for some of the things, and some of the discussions that have to take place. C-Path won't develop drugs or medical products. We will work on the process.

As happened with the Food Center--the National Center for Food Safety and Technology--we believe is a proven concept. It was established

over 15 years ago as neutral ground. And in their website, the Moffett Center is described as "neutral ground where industry, academia and FDA scientists work together to address food safety. And that was the model that we were aware of and used as we created the Critical Path Institute, or C-Path.

It's neutral territory, publicly funded. Industry consortia can fund projects if it's done with the industry and FDA come together and agree, as they do in the Food Center, that there's important work that needs to be done. And that would be done with transparency and oversight; project-specific funding; oversight board with the FDA, industry and consumer and patient representatives should be present.

[Slide.]

We believe that PDUFA, as I said, has uncovered this other problem. And the FDA has

issued its White Paper, and it's willingness to work and partner on this. But there are some missing ingredients. A very big one is the lack of funding for the FDA to participate. How can they have the staff to work on these projects and attend these meetings? They need the internal funding.

And then there needs to be a funding for the method development and validation that's part of the call in the Critical Path Initiative.

Most industries invest 5, to 10, up to 15 percent of their annual budgets into changing the process that they use to make their process. So we believe that that kind of funding into developing the process--it's not, as I've said in other audiences--it's not sexy. You won't get an NIH grant for this. You won't get tenure, or you won't get publications for this kind of work. But it is essential in the development of new medical products.

There's also a lack of a process to prioritize and coordinate the Critical Path Initiative activities. That's something that needs

to be funded.

There's also at this time a lack of an understanding of a laboratory for testing new methods and biomarkers. Many companies don't want people experimenting with their products as they develop new methods. So we've got to find a way where we can test those new methods in an acceptable environment.

So the proposal that we have--on the next four slides--

[Slide.]

--if Critical Path Initiative funding should be made available to the FDA, perhaps a small percent increase in the PDUFA fees, to fund the work at the FDA, with a match from Congressional appropriations, so that the Agency would have the funds to hire the staff to do the work on the process that needs to be changed.

[Slide.]

The funding for the methods development and validation also needs to be obtained. And, there again, industry consortia, operating with FDA

advisors on, we think, neutral ground is important for that. We think that there needs to be a tie-breaker when the industry and the FDA may disagree about how to go forward with the process. Outside scientists can help generate the consensus for which methods need to be tested, and how.

[Slide.]

PDUFA grants and contracts for work mutually agreed upon by a CPI--Critical Path Initiative--steering committee would be one way to do that work.

[Slide.]

Ad how do you develop that process? We suggest using the Moffett Center model, where there's an oversight board, with FDA representatives, industry representatives, consumer/patient reps, and independent scientists and experts who work outside of the environment of the regulators and the regulated.

[Slide.]

And the testing environment is perhaps the most difficult area, but I would like to suggest

that in life-threatening illnesses, many of the technologies could and should be applied to accelerate the development of safe drugs; orphan drug development. This is an area where Congress mandates the FDA to assist in the development of orphan drugs. Why not have that applied more broadly to all drugs, especially those with life-threatening illness, and for personalized medicine. I would suggest, and perhaps, others be considered as the laboratory for where the process of drug development, or medical product development can be applied.

[Slide.]

In summary, the regulators and the regulated, I believe, need neutral ground where they can work together to improve the process of drug development. I think PDUFA could be the catalyst for this change, and a shared investment by government and industry would be the way to do that.

Thank you.

MS. HENDERSON: Thank you, Dr. Woosley.

Our next speaker is Dr. Ernst R. Berndt. He is the Louis B. Seley Professor of Applied Economics at the MIT Sloan School of Management,

and co-director of the Biomedical Enterprise Program at the Harvard-MIT Division of Sciences and Technology. He's also the director of the National Bureau of Economic Research Program on Technological Progress and Productivity Measurement, and co-director of the Center for Biomedical Innovation at MIT.

Of particular note, much of Professor Berndt's recent research has focused on price, output and outcomes measurement in the health care industries, and on regulatory policies at the U.S. FDA.

Dr. Berndt?

DR. BERNDT: Thank you.

I have more slide material than I have time to discuss, so I'm going to skip through a number of the slides. You should have in your packets, however, a complete set of the slides.

Today I'm going to talk about, briefly

summarize, results from two recent research projects.

[Slide.]

The first was published this summer in a peer reviewed journal, Nature Reviews: Drug Discovery, and the second is soon to be published, but is publicly available, and if you want a copy, please let me know.

[Slide.]

Why PDUFA? Other speakers have discussed this briefly already. FDA, as you know, has two missions: one is to assure safety and efficacy of therapeutics; and the second is to help speed access, or marketplace access, to innovative therapies. And it was this second mission which seemed to be less completely fulfilled. You can see here that if you, depending on what particular two years you choose, you can see quite an increase here in terms of review time, from 22 months in 1970, to over 32 by 1990.

In response to that, Congress addressed the issue by passing a serious of Prescription Drug

User Fee Acts, in 1992, 1997 and 2002.

[Slide.]

And at least if you look at these rather quickly--this is a study that was published by a Tufts research--there appears to be a decline in the approval time at the FDA.

[Slide.]

Now, I should mention that under the PDUFA legislation, all that was mandated is that the FDA review and act on applications. This did not necessarily translate itself into more rapid approvals; simply "act and review on."

And so the issue is: how are these linked? I might add that, as several of the speakers have mentioned, and as a White Paper that was released a few days ago emphasizes, to date the user fee program has been very important for funding at the FDA; roughly about 50 percent of money spent in review of human drug applications--I think it's up to 52 percent this last year--emanate from PDUFA.

And, as Dr. Gottlieb mentioned, user fee programs have long been elsewhere. We've had it in

the U.S. patent system for centuries, and we have it elsewhere in the world. The EMEA that about 75 percent of its funding come from industry fees. The U.K. is funded entirely through user fees. Japan has no user fee program.

[Slide.]

All right. So, for the first set of issues we wanted to ask is: to what extent have PDUFA I and II been associated with incremental reductions in NDA/BLA review time, controlling for other things that were happening, like patient advocacy groups, change in the composition of therapeutic class applications, and so forth.

Secondly: what is the effect of PDUFA on safety withdrawal rates?

And thirdly: what would the time trend of NME approvals have looked like in a world without PDUFA? Would the R&D slowdown have improved, or would it have been exacerbated?

[Slide.]

The research methods we employed in this first study were using the universe actually of 662

NMEs that were approved by the FDA between 1979 and 2004. And we used what's called multivariate regression analysis. And I won't go through the details of that here.

[Slide.]

These are just some of the explanatory variables that were employed. You certainly don't want to spend too much time on this, but if you look at the upper right-hand corner, the basic result is that while approval times at the FDA had been declining a bit pre-PDUFA, about 2 percent a year, during PDUFA I this accelerated to about 10 percent decline per year. Then, during PDUFA II, they continued to decline, but at a lower rate of around 5 percent a year; so, clearly, suggest that PDUFA is associated with shorter review times.

[Slide.]

You can simulate them using the estimated model: what would the world have looked like without PDUFA? As you see here, if you look at, fore example, when PDUFA came in, that was about 24 months review on average. Had PDUFA not been

implemented, that probably would have declined, at least the model predicts, to about 20 months. In fact, however, it declined to less than 15 months.

[Slide.]

I think is probably one of the most interesting slides of this presentation. What we did is we said: let's assume that the dates on which applications were filed at the FDA was unaffected by PDUFA, but that the previous sort of track record would have continued on. What would have happened instead?

This is the number of new drug, or NME approvals, that actually occurred, in blue, versus what would have happened had PDUFA not been implemented, in orange. And what you see basically is that whole curve is shifted to the left. By 1997, for example, in the bottom of this figure, we say what's the cumulative number of NMEs that were approved, by 1997, at the end of PDUFA I, had PDUFA not been implemented, the model predicts that only 187 drugs would have been approved, whereas, in actuality, 220 were. So that's a 15 percent

acceleration.

By 2002, 389 drugs were actually approved. What would have happened in the absence of PDUFA is about 376, about 3 or 4 percent less. So you see this backlog that was basically filled out and much more rapidly acted upon in response to PDUFA.

And the bottom line, then, is that effectively what PDUFA did is it meant that many patients now had more rapid access to innovative medical treatments.

Now, what about safety?

[Slide.]

We can compute safety withdrawal rates, and there are only three problems that I can think of with safety withdrawal-rate calculations. One is the numerator; two is the denominator; and three is the time span. Other than that, they're just straightforward.

So--numerator. What constitutes a safety withdrawn, when a drug is withdrawn and then reintroduced later on under more strict conditions, is that a withdrawal or not?

Denominator--what sample of drugs should be included? Biologics? Vaccines? Radiologicals? Annual vaccines? There's some ambiguity there.

Third, the time period definition--what defines "pre-PDUFA" and "post-PDUFA?" Is it when drugs were approved? Or when drug applications were submitted?

You can move these numbers around a fair bit. Because withdrawals are so relatively rare, you can move these numbers around quite a bit just by using calendar year versus fiscal year, and a variety of things like that. And one should bear that in mind.

With that caveat, let me just mention three studies.

[Slide.]

One was a study published by the GAO, and focused only on chemical entities, not biologics. And although they didn't actually do the calculation, we used their numbers and calculated that there was no significant difference between those calendar years '86 to '92, versus '93 to

2000.

There was an internal FDA analysis that was also put out. And, again, you can do a test on whether there was a significant difference in terms of approval dates pre- and post- PDUFA; withdrawal rates based on approval. Again, no significant difference.

And we did a study of that, as well.

Now, all these studies suffer from the problem that there's differential time on the market. Drugs approved before PDUFA have been on the market much longer, have had greater opportunity, if you will, to experience safety issues. And so what we did was do a survival analysis, which folks, I'm sure, in this audience, know very well, a Kaplan Meier curve.

And I'd like you to look at two things here. Basically, the dark blue is the cumulative survival rate pre-PDUFA, and the more purple one is the post-PDUFA.

Notice two things: the first thing is they tend to converge after about 12 years on the

market. And, secondly, notice how--I mean, this graph kind of accentuates the difference because it starts at 97 percent, not zero percent--notice that drugs, at least in terms of calendar time, are now being withdrawn from the market more rapidly. Whether they're being more rapidly withdrawn in terms of exposure to patients is not clear, and is worthy of some examination.

[Slide.]

This slide just simply points out that drugs that were withdrawn from the market are now withdrawn much more rapidly; the mean of 2.4 months post-PDUFA, compared with 5.19 pre-PDUFA.

[Slide.]

Okay, let me switch to the second paper. As Dr. Kaitin and others have mentioned, while there's been an admirable success in reducing review times and approval times at the FDA, we can't say the thing about what's happened to clinical development times. These things haven't budged for 25 years; still about six years.

And so what I did with some of my students at MIT is we decided to interview 50 senior R&D folks at a variety of biotech and pharma companies,

as well as a few CROs, and we also interviewed eight senior staff members at the FDA. This was all done in the first half of last year, prior to Vioxx withdrawal and the anti-depressant hearings.

It was pretty evenly divided between biotech and big pharma. And we asked them what can be done to make the clinical development time more efficient? Is the FDA a problem? Is the industry a problem?

And basically we've written up these results at some length. Let me just talk about a few of the questions we asked.

One was that we asked industry whether they thought FDA was doing a good job in terms of preventing unsafe drugs from coming to the market. There was general feeling by industry that the FDA was doing a good job of that. I would say the industry had "guarded respect" is probably the right choice of word to use.

However industry also believed that in a number of cases there were significantly delayed review times that ultimately had a substantially negative impact on the public health.

I might add that in this thing we didn't interview legal counsel or CEOs, or CFOs. This was

senior R&D folks, who might have a different view than others.

[Slide.]

Now, more germane to this particular hearing, we also asked questions to both industry and the FDA: where would additional communications with the FDA be most valuable? And what was sort of interesting: industry believes that additional communications and interactions with the FDA would be very valuable across all phases of the development process, from pre-clinical IND to Phase I, Phase II, Phase III, and the actual NDA.

By contrast, in four of these five stages, the FDA rated the value of additional interaction much lower--significantly lower--than industry. In one case, however--and I think it's a very notable

case--the FDA and industry agreed that additional communication would be very valuable: that was early on in Phase II, particularly with respect to dosing issues.

[Slide.]

And much to our surprise, industry seemed to be willing to put their money where their mouth was, at least the R&D directors were. And industry interviews indicated that 'Our company would be willing to pay PDUFA type fees" particularly in Phase II. If you look at that, 80 percent--or 990 percent all together--were willing to pay more than $100,000 for additional contact with the FDA.

The FDA working paper issued over the weekend indicated that, in fact, there have been a more meetings--I think they're called Class B meetings, in particular. And that suggests to us at least, on this project, that there might be some very fruitful discussions with industry and the FDA in terms of using additional user fee program to fund Phase II meetings.

[Slide.]

We had a number of recommendations that came out of that, as I just mentioned. Two of them were to institute better metrics and goals for

development in exchange for PDUFA-like fees; increase interactions prior to Phase III, funded by user fees. I have a friend at Harvard University, Dan Carpenter, who's also just written recently suggesting that user fees might be tied to post-launch surveillance issues. We did not ask those questions in this survey, nor did we link user fees to DDMAC approvals of advertising content. But those are issues that might very fruitfully be discussed.

[Slide.]

Finally, we've done some additional work in this area that tries to monotize some of these benefits and costs of PDUFA. That's now in the peer-review process. If you want a copy of that paper, you can download it from te National Bureau of Economic Research.

Thank you.

MS. HENDERSON: Thank you very much, Dr.

Berndt.

Finally on this panel we have Dr. High Tilson.

After retiring from GlaxoWellcome in 1996, Dr. Tilson joined the full time faculty of UNC School of Public Health in Chapel Hill where is a clinical professor of public health leadership, adjunct professor of epidemiology and health policy, and senior advisor to the dean.

In addition, he is adjunct processor of social medicine at UNC; medicine at Duke; and pharmacy at UNC.

He is an advisor to government and industry in health outcomes, drug safety, and evidence-based health policy, including most recently public health preparedness.

Of importance to the topic at hand today, Dr. Tilson chairs the National Steering Committee for the Centers for Education and Research on Therapeutics--the CERTs program.

Dr. Tilson.

DR. TILSON: Thanks, Madam Moderator. And,

in fact, thank you for actually giving my talk. My reason for being here is to let you know that the Centers for Education and Research and Therapeutics--the CERTs--are here to help you.

In fact, I have three very simple messages. The first is: the CERTs belong to the FDA, and the FDA needs to use them.

The second is: the CERTs belong to the FDA, and the FDA needs to build them.

And the third is: PDUFA provides an extraordinary opportunity for the FDA to leverage its work with the CERTs even more than it has up til now.

It's wonderful that I get to be the last member of this panel, because I get to bring you a terrific success story. I'm very optimistic about what the CERTs have already been able to achieve, and the promise here, particularly in the face of renegotiating PDUFA, is quite extraordinary.

The CERTs were part of the second regulatory revolution. If PDUFA was the first, then certainly the FDA Modernization Act--or

FDAMA--was the second. And the CERTs were created by the FDA Modernization Act in 1997, specifically by act of Congress, to extend the public health role of the Food and Drug Administration through education and research, beyond simply the regulatory stick.

While directed to the Food and Drug Administration, it is administered by AHRQ, through an extraordinary partnership between AHRQ and the Food and Drug Administration--more about that in just a second.

We have seven centers out there already, with four more currently being considered, and shortly, I hope, to be approved and reported. And that gets us about halfway there to the total number of 22 which, at least our steering committee feels, the nation needs. There's an opportunity for PDUFA if there ever was one.

We have almost 300 projects up and going. And if there was ever a success story, it was the public-private and public-public partnership that was part of the FDA Modernization Act mandate, with

over 130 partners working with these seven centers. And over 200 peer-reviewed publications--obviously publications aren't the output; improved health is the output. And so one of our accountabilities is: so what?

[Slide.]

Let me just touch on the Congressional authorization. You my handout, and I don't plan to read this slide in any great detail, except to point out that in its wisdom, I must say added by Ray Woosley who is a member of our CERTs steering committee, the Chair of the Arizona CERT, and one of the inspirations for the CERTs movement, Congress realized that we have to have research in order to communicate more effectively, then we have to communicate more effectively and have research to document that we have done so, and provide the objective clinical information to all of those in the decision making system.

Finally, of course, and quite critically, Congress also suggested that we have to have research on comparative effectiveness,

cost-effectiveness, and safety of drugs, biologicals and devices--some of the things that a marketplace funded primarily by the research-based pharmaceutical industry simply can't and won't do by itself. And it represents a significant new role for the Food and Drug Administration, mandated by FDAMA, but not funded yet through PDUFA.

[Slide.]

The model for public-private partnerships is shown on the next slide. And again, without going to great detail, let me just point out that public-private partnerships are taken deadly seriously by the CERTs. We have a mechanism to review them and ensure the independence and trustworthiness of the academic process that gets brought to bear on this process, without turning our backs on industry, regulatory and commercial partners, who know more about the subject than we may, and certainly have a major stake.

So creating the ground rules for this--the "neutral harbor," to use the term that's already on the table--was a critical objective for CERTs. And

we created a vision statement to reflect that; namely, "to serve here as a trusted--"--with that as the operative term--"--a trusted national resource for all the people who are seeking to improve health through the best use of medical therapies.

[Slide.]

This organigram simply documents the points that I've made. The Food and Drug Administration work collaboratively with AHRQ to oversee this program. There is a coordinating center located at Duke, and seven centers which work collaboratively with the coordinating center, listed here, including Arizona CERT. And there should, of course, be a dotted line out there to the C-Path Initiative, which is one of the CERTs partners, co-located by and fostered through the University of Arizona; the University of Pennsylvania, Vanderbilt, University of Alabama at Birmingham, the University of North Carolina--go 'Heels!--and the HMO Research Network, as well as Duke University, a separate CERT.

This entire process, however, is guided by a national steering committee, upon which the Food and Drug Administration, AHRQ, and the Centers for

Disease Control all participate. There's also at-large public participation, most recently through the National Health Council, and before that, through the National Consumers League; and professional oversight, most recently through the American Nurses Association, and currently through the American Public Health Association. And big pharma has a seat at the steering committee table as well because, of course, they are essential partners in moving this forward.

[Slide.]

The next slide shows the inventory of centers, and I leave that to your reading. But suffice it to say: centers, in addition to be generalists in improving the nation's therapeutics, have their own areas of specific focus and expertise, ranging from infection control to addressing the problems of children.

Incidentally, watch this space for the

announcement for the next four CERTs which will include, among others, one in the long-neglected area of devices, and another critically needing advancing: that is the consumer perspective, particularly risk and benefit communication involving consumers.

[Slide.]

Well, all right. So what do the CERTs bring to this table? And why is this an item for PDUFA?

Well, the answer is: the CERTs do research. And here is an inventory of the sorts of research the CERTs do: patterns of use; inappropriate, unsafe use; understanding risk management; documenting that risk management tools may or may not be effective, and how they might be effective; and particularly, of course, apropos of Steve Galson's critical comments, safety surveillance methodology, in partnership with the Food and Drug Administration.

[Slide.]

I list a couple of examples on the slides.

And I don't want to go into them in any great detail. I just wanted to put some flesh on these bones, looking at something as important and expensive as transmyocardial revascularization, for example. To understand when it is used appropriately, and when it is not, will help the Centers for Medicaid and Medicare Research decide whether they do or don't wish to fund, and under what circumstances. So being a partner with CMS represents a critical dimension for the CERTs, as well as partnering with other Federal agencies.

Here the possibility of monitoring patterns of use will help us to understand and learn from off-label use. Off-label use isn't good or bad. It's just off-label, and it represents use without the data available, and therefore a great opportunity for us to use PDUFA funds to learn from that experience.

[Slide.]

FDA is co-sponsoring some work with the CERTs that is extraordinarily important, I think, looking critically at the large automated

population-based data sets out there. HMO Research Network is one of our seven CERTs, for example, and has the population of the sixth largest state in America of covered lives, for whom we have automated data of all prescription drugs, and all major medical outcomes. And yet we don't have a proper demonstration of their value in generating and documenting signals of possible adversity in drug use. Well, Food and Drug Administration is partnering with us to do so.

And Ray Woosley pioneered the QT drugs registry, and from that a tremendous groups of learning opportunities, including curricula for medical education.

[Slide.]

CERTs are a convener. We've convened a series of think tanks, workshops. And it is said by many of our colleagues at the Food and Drug Administration who collaborated on five, looking at risk-management, its communication, assessment; working with media and the risk; balancing benefits against risk and so forth--that this thinking from

these workshops and think tanks was instrumental in helping the Food and Drug Administration to develop its response to Congress for a program of guidance for risk management.

[Slide.]

All right. So here's the inventory of the things that I've said; represent things that Food and Drug Administration, as it contemplates PDUFA, particularly in the face of the drug safety work, which you already heard from Dr. Galson represents great progress, but a work in process, needing more work, might wish to pursue.

Particularly here, the Food and Drug Administration has an extramural grants program to fund research in the development of methodologies and tapping into large automated population-based data bases, the so-called extramural program. Its external advisory board--I've sat on several of those study sections in my own jaded past--has recommended for years that that program is not simply underfunded, but it's underfunded by an order of magnitude; that is, a million dollars

barely skims the surface; $10 million might help.

And, of course, finding a partner to do the work with you; the partner who understands the use of population-based data and can work at arm's length as a trusted resource, represents the way forward, in my view, for PDUFA.

And therefore, here's our critical path. It's working together. The CERTs are there. Use them. The CERTs are yours. Build them. The CERTs represent an opportunity for PDUFA. Fund them.

Thank you.

MS. HENDERSON: Thank you, Dr. Tilson, very much.

We will now take a 10-minute break. I will ask all of you to be back in your seats by 10 minutes after 11. And I'd ask our third panel, which includes Dr. Cohen, Ms. Dorman, Dr. Sigal, and Ms. Ireland to be seated and ready to go at 11:10.

Thanks a lot.

[Off the record.]

MS. HENDERSON: Back on the record.

If you'd begin to return to your seats so we can get started. This panel is between you and lunch.

[Pause.]

Okay. If you'll take your seats, we'll get re-started. It may look like our FDA listening panel has emptied out. But, in fact, it's not true. Just for the information of the audience, some of our panelists have asked to move to the audience so they can see the slides for the presentations better.

Panel III - Presentations by Patient Advocacy Groups

MS. HENDERSON: We're going to change the order a little bit of this panel to accommodate Ellen Sigal's schedule. So we will move Dr. Sigal to the beginning, followed by Dr. Cohen, Ms. Dorman, and Ms. Ireland.

And we will start with Ellen Sigal.

Ellen Sigal, Ph.D., is founder and chairperson of Friends of Cancer Research, a Washington, D.C.-based nonprofit organization.

Friends is dedicated to accelerating the nation's progress toward prevention and treatment of cancer by mobilizing public support for cancer-research funding, and providing education on key public policy issues.

Dr. Sigal serves on the National Cancer Institute Board of Scientific Advisors, the National Institutes of Health's prestigious Director's Council of Public Representative, the National Institutes of Health Foundation Board, chairing its Public-Private Initiatives Committee, the American Society of Clinical Oncology Foundation Board, the American Association for Cancer Research Foundation Board, the Johns Hopkins Cancer Center Advisory Council, the Duke University Cancer Center Board of Overseers, and the Howard University Cancer Center Board of Visitors.

So we are very pleased to have Dr. Sigal with us.

DR. SIGAL: Good morning. And I'm sorry about leaving early, but I'm on the Board of Scientific Advisors of the National Cancer

Institute, and there's a critical vote that I need to participate in. So I will try to be brief, and I will try not to be redundant, although some of my slides are redundant. But I will try.

[Slide.]

So why do we care, in the cancer community? That's pretty obvious. I mean, obviously, we have a million-three patients impacted every year on this; over 500,000 people dying every year of this disease. And, frankly, until many years ago, many of us in the advocacy and the research community didn't really focus on the FDA. It was a big black hole that was seen to be insurmountable, unintelligible, and frankly to many of us, dysfunctional. And frankly, there were a lot of bad drugs, and there not a lot of opportunities. So you know, that was the prevailing view.

And a few years ago that changed. That changed. We thought that we really had a stake in the FDA, because we talk a lot about translational research, and you can't translate anything until

you have better drugs, and more effective drugs. And so we started to work with the Agency in a very collaborative way. And now, rather than a black hole, they have become friends; people we care about. They're extremely, extremely important to the new generation of drugs, and to all cancer patients.

So we have a major stake in the FDA. So we care a great deal.

I'm not going to go over PDUFA. You all know about PDUFA. You know more about PDUFA than I do. You've heard about it today.

Evaluating PDUFA is important. You know, I think that we're trying to, with the renewal of PDUFA, there's going to be a lot of metrics for evaluation. We heard some really good data today.

By and large, it's very, very successful. And I think any of the critics that are going to complain about safety or compromising integrity are not going to be very happy, because the data shows the opposite. So PDUFA has been very, very good thing for the patient community, and certainly for

the cancer community. And we are enthusiastic about the continuation of PDUFA and, frankly, the enhancement of PDUFA.

[Slide.]

You know, PDUFA has allowed the FDA to expand the user fees for the management. It's added staff. And, again, it's helped understand drugs' risk profile, which I'm going to talk about in a little bit.

[Slide.]

The safety issues are a very dramatic concern to the cancer community. This is something that we are very worried about, because we think that the cancer community can be more dramatically impacted on an overzealous of safety, or interpretation or understanding of safety, and therefore we often say: safety kills. And we mean that. I mean, we're very concerned about a new pipeline of new and better and targeted drugs that will really make a difference to the patient. And if we get so consumed with safety we, in fact, will lose many, many, many more patients from this

disease than not monitoring safety.

So it's extremely important for us. And we have patients from all ends of the spectrum; from people who have, you know, what can be a chronic disease, and people who have diagnosed with fatal disease. So clearly these issues are of significance. I mean, clearly, I'm going to tell you the obvious: no drug is 100 percent safe. And that we know about. And the public needs to understand that. As a matter of fact many of the nutriceuticals that people are taking in large quantities are not safe, as well. So they need to understand that.

So obviously this issue between risk and benefit is very important. Intelligent design of trials. And if the speed and the certainty of drugs is really what we care about. We certainly understand that we need to monitor drugs; that we need safe and effective drugs. And particularly as our disease becomes, hopefully, a chronic disease, this is going to be even more important.

So clearly, really, safety and efficacy

are extremely important.

[Slide.]

There are things that can be done on safety. None of us would suggest that we're doing enough, or that we can't do better. But we need the resources to do that.

We are very worried about overzealous regulation that would only deal with safety and create more bureaucracy and infrastructure and really not deal with efficacy. But we can certainly collect more data. We can enhance the Med Watch. We can increase the FDA's capacity to process and analyze adverse events and get that information to the public.

But ultimately these decisions are between the patient and the doctor. And we don't want on-size-fits-all. It can't work for cancer, and it shouldn't work for cancer. We want these decisions. We want the information. And people are going to have to be informed about their choices on these drugs.

[Slide.]

Looking forward to PDUFA IV, clearly we talked about the safety of drugs. And I think that can enhance. And if we can really deal with the

funding of FDA, and the funding of PDUFA, I think that that's going to be critical to the cancer community, and to the patients' receiving treatment or diagnostics.

Funding is important. I'm going to talk about that a little more later on. But efforts to enhance safety systems should not compromise the timely approval of many patients facing life-altering disease. And this is the consistent message that I want to discuss.

[Slide.]

Adequate Resources--that's a huge concern. FDA is one of the most underfunded agencies in the Federal government. And I don't think people understand that. And I think people need to understand that. PDUFA isn't going to entirely fix it. As a matter of fact, it's a danger. We have to be very careful that we continue to fund what we're supposed to do for FDA, and fund the science,

integrated the critical path, and to really fund the agency appropriately. And that's very important.

That doesn't mean that we shouldn't continue to do PDUFA. We should enhance it. We should look for perhaps other funders other than the pharmaceutical agency, because I do think that even foundations and patient groups--there are other sources out there for funding and we should explore them. But we must continue continuing to appropriate the FDA and, frankly, enhancing that, because that's going to be important.

And we really have to look at the critical path and the funding mechanisms for the critical path. Because if we don't integrate the science and fund the critical path, we're not going to get better and safer drugs to patients. So this is a very important issue.

[Slide.]

Finally, what's important to us is that our disease, or cancer, is changing. We have a lot more information. WE have better information. WE

will have better drugs. They will be more targeted. They will get to the patients faster, we hope, and they will be more effective. So continuing the science, integrating the science, working collaboratively with the NIH, with the FDA, and with patient groups is critical to this.

So we are very enthusiastic and, frankly, consumed with what happens at the FDA. Because what happens at the FDA impacts everyone who will be diagnosed with this disease, and everyone treated with a disease. And it's much more than just, you know, people who have final forms of cancer. We're talking about diagnostics, we're talking about a better class of drugs, targeted drugs.

So this is really a new day for cancer. And if we're going to achieve the 2015 goals, and if we're going to really help cancer patients, the integration of science, safety, the funding is going to be critical to us. So we care a great deal about what happens, and we're very vested in it.

You know, clearly a stronger FDA helps all of us. The predictability, the consistency of the application, greater efficiency. And frankly we

need, in the patient community and the research community, to do a better job of advocating for the importance of this agency. I think a lot of people have really only talked about the science and the research. We just spend a lot of time talking about translational research, but not enough time about the entire spectrum, from early diagnosis to the importance of the interactions with the NIH and the FDA.

As a matter of fact, when Mark McClelland came to the FDA, and Andy von Eschenbach, the first thing they did is this interagency task force between the National Cancer Institute and the FDA. And we encouraged that.

We'd like to see advocacy groups and patient groups and industry and CMS as part of that, as well.

So we want innovation. We want better science, and we care a lot about what's happening.

And PDUFA IV is going to be on our radar screen. And the FDA is not a black box to us any more.

Thank you.

MS. HENDERSON: Thank you, Ellen. We'll let you set off to your vote.

Our next speaker is Dr. Perry Cohen. Dr. Cohen is an active participant and leader on the national level in advocacy activities for Parkinson's issues. He is project director for the Parkinson's Pipeline Project, which he initiated to provide the patient's perspective to clinical researchers and sponsors of new therapies.

Prior to diagnosis with Parkinson's disease in May of 1996, Dr. Cohen was a planning and evaluation consultant in the health industry for public health agencies, health insurance plans, and academic research centers. He has an M.S. and a Ph.D. in organizational development from MIT's Sloan School of Management, and a Bachelor's in Management Science and Math from Carnegie Mellon University.

Please welcome Dr. Cohen.

DR. COHEN: Thank you. And thank you for inviting me.

As you introduced me, I am a Parkinson's

patient and advocate, and I've had Parkinson's disease for 10 years now, and it gets worse.

But I've been patient representative at FDA for Parkinson's since on a was on a deep brain stimulation advisory panel back in 2000. And in this role I learned some of the things that he last speaker just talked about, about the FDA. And I set up the Parkinson's Pipeline Project, which is a grass roots effort, to do everything we can do as patients to speed up and facilitate introduction of new treatments that are leading to cures.

[Slide.]

A little bit about Parkinson's Disease: briefly, in case you don't know, it's a chronic degenerative neurological condition, characterized by the loss of dopamine neurons. And dopamine is what controls movement. But it's interacting with other parts of the brain. The brain is very complicated, as you know. And there are cognitive

and emotional symptoms, as well as autonomic system functioning, such as breathing and swallowing and some of the other aspects of Parkinson's.

Parkinson's is known as a lower prevalence chronic disease by CDC, with somewhere under a million patients. It's far fewer than the bigger chronic diseases such as heart, cancer and diabetes. But it's similar to, like hundreds of other neurological diseases, which I think the next speaker will speak about some more. And collectively these numbers probably add up to a significant public health problem, which is only beginning to be recognized.

And Parkinson's is on the vanguard on the last frontier of science: the brain and the central nervous system. And if the neuroscience meeting, which is downtown, which I have to go to later today, is any indication, we should be having more active discoveries and treatments in the future.

Another thing about Parkinson's is: we have a pretty active advocacy movement. And there's a number of celebraties and prominent

business people, as well. And just to let you know, for the advocates, there are a lot of people in the closet still who you'd be impressed to know have Parkinson's disease, and are starting to creep into the advocacy work.

[Slide.]

As far as treatments and cure goes, it's sort of a good news and bad news situation.

First identified in 1817 by James Parkinson, the science and treatment has advanced compared to other central nervous system conditions. The good news is there are many effective treatments for Parkinson's. The bad news is the treatment may stop working after five or 10 years, and the side effects of some of these treatments are as bad as the symptoms. So we need more development.

The good news is there's more known about Parkinson's than any other brain disease, and the recent big build-up in science has put us on a path toward better treatment and cures that are promised to be right around the corner. They've been

telling us "five years" for the last 15 years.

The bad news, however, is the pipeline, which we've been talking about today, 15 or 20 years or more--and I was quite impressed with that figure of neurological conditions, clinical pipeline average of 11 years. And I want some of the academics who spoke in the last panel to address that issue really quick.

But in addition to the scientific issues, there are financial markets, and business strategies, and organizational politics, and people's careers, and publication schedules and all these other things that are in between us and the cures and treatments that we need.

[Slide.]

So, what do patients want?

First: faster cures. Time is not neutral for someone with a serious or life-threatening illness. And we want to look beyond the review time. We want to look at the whole process; the whole process of drug development, and look for ways to do that.

I've learned a lot at this session. These slides were obviously prepared in advance. I've learned a lot about what's being done. And I have

to admit I was not fully aware of everything that was being done.

And second, we want more emphasis on individual decision-making and choices--sort of echoing the last speaker. We need to recognize that the equation of risk-benefit tradeoff is different for each person, and there should be more flexibility for individuals to make their decisions, with advice and counsel of their own physician, or some expertise; but also with full information. And that's the key. Some of the safety problems, the coverup is worse than the problem.

And third, we want greater participation in the process. We're not rats in a cage. Our experience is valid, and it's often not captured or considered. And I've been working with several companies, and this is true.

[Slide.]

Here's my naive view of what PDUFA has done--before I got here today; which is basically correct, but now I know a lot more.

The PDUFA was established to reduce the length of time in reviews. There's extensive industry consultation, and FDA agrees to meet

performance standards. And there's been little or no input from patients and consumers in the past legislation.

[Slide.]

So here's my view of the patient perspective on user fees, from the outside looking in.

As I said: little information on the time frames, on the processes. It's a black box. The FDA processes are a black box. And even when you're involved with specific treatments, the proprietary information of the companies seem to be more important than the distribution of the scientific data. And when there are meetings, we don't even know when the meetings are being held, or if they're held, much less what goes on in them.

There are a couple of simple observations I would like to make. The user fees are now greater than 50 percent of the FDA review costs, as was presented earlier. And this raises questions. Now, I don't believe this to be true, but it raises questions in the press and in the eye of the public, whether there's a lack of objectivity related to the rulings, based on this dependence on fees.

So it behooves us, as advocates, to lobby for the FDA budget, just the way we lobby for the NIH budget, and with great success. So I'm not sure if the Agriculture Committee in the Congress has enough appreciation of what the FDA does. And, unlike the rest of the Health and Human Services Department, the FDA budget is handled by the Agriculture Committee, which came as a big surprise to me.

Another little technical point is that the fees are only paid when the new drug application is submitted, yet the costs are distributed throughout the process. And that was pointed out earlier, as

well. And by doing so, I think that maybe explains at least part of the reason why there are fewer applications.

[Slide.]

So we do we have for suggestions?

My view is that we have an untapped resource, and there are new roles for patients. The Office of Special Health Initiatives, which included me and a number of other patient representatives and patient consultants, has been cultivating and advocacy group. And I think this is important for several reasons.

First of all, when you have patients at the panel, that could counter the appearance of a bias towards industry if the patients are actively involved, because everybody says the bottom line is the patient's safety, and the patient's treatment. And if the patient is at the table, then you get that viewpoint expressed.

[Slide.]

Next, it needs to be a transparent process. Information about the process needs to be

more public; when they're having meetings, what stage of the process they're in. Certainly, companies are allowed to have proprietary information, but if we knew what was coming down, if would give us something to have some hope for, and something where, if we were involved in the process more, we could contribute to.

And I think the FDA should expand the excellent efforts of the Office of Special Health Initiatives to support community groups like the one that I work with, in education of the community about the regulatory process.

[Slide.]

So, just to summarize, this is our motto: "The missing ingredient in new therapy development is the voice of the patient."

We're partners in clinical research. We're seeing input in risk and benefit judgments. And awe have created a research participants' "Bill of Rights," which sets a framework for collaboration in relationships between industry and researchers and patients. And PDUFA should

recognize these roles.

[Slide.]

Now, a couple more suggestions. And this has been covered earlier quite a bit, so I'll go over it quickly. The entire pipeline should be examined for time savings. And system changes are necessary to achieve significant reductions in the duration of the pipeline, and the maintenance of the quality. These have been brought up in other talks quite strongly and I would agree with that.

[Slide.]

Business and science as usual is not sufficient. Though we have some leadership, the Critical Path Initiative, which has been mentioned quite a lot, the NIH translational research road map, they're talking the terms--the system's terms. And my training in management and organization and systems, it seems to me that they're talking the way to go.

And "Faster Cures" is a program that starts looking at some of the assumptions in business-as-usual, and science-as-usual--like cycle

times have been mentioned here; and turnaround times in getting the information back into the process from scientific research.

[Slide.]

And finally, I think my last suggestion is we should view the process in the continuous quality improvement paradigm. Rather than have one giant step to approve, which may make people be more cautious, I think we need a series of shorter steps of conditional approvals that expand the markets and the target audience for research in a more gradual way, and that way you could get some early approvals, particularly for those people who need access to potential life-saving treatments, as well as then continued maintenance of control of some of the bigger safety problems that might come up down the road.

And that's all. Thank you.

MS. HENDERSON: Thank you, Dr. Cohen. We very much want to hear the voice of the patient, and surely appreciate your input.

Our next speaker is Dianne Dorman. Ms.

Dorman currently serves as vice president for public policy for the National Organization for Rare Disorders, also known as "NORD," where she develops and maintains relationships with Federal agencies, including the National Institutes of Health, the Food and Drug Administration, and the Centers for Medicare and Medicaid Services, the United States Congress, the biotechnology and pharmaceutical industries, and other health care-related agencies.

Ms. Dorman's efforts include work with other patient organizations and coalitions to accomplish initiatives that benefit people with rare diseases. Technical assistance and legislative analysis are provided to NORD's member agencies on government-related matters, as well as the training of staff and volunteers of member organizations.

Thank you for being with us--and you're on.

MS. DORMAN: I want to thank the FDA very much for giving me the opportunity to speak to you

today about the impending reauthorization of PDUFA.

I'm going to be focusing my comments on a user fee issue that is very specific to the development of orphan products for patients in the U.S. affected by rare diseases. It is an issue that is of extreme importance to NORD and the people that we represent.

Now, for those people who may not know what a rare disease is, it's any disease that affects fewer than 200,000 people in the United States. And that's based on statute, the Orphan Drug Act, which was signed into law in 1983.

[Slide.]

I want to go back--if those people who may not be familiar with the statutory provisions of PDUFA as it relates specifically to orphan products. The companies do not pay one-time application fee for orphan drugs. The orphan drugs qualify for waivers of annual product and facility user fees if it is perceived that there is an unmet need, a public health need; or the fees would be a barrier to innovation; or if the company qualifies

as a small business. And the waivers may be partial, or they may be complete. And that is how it's written into the PDUFA statutory language.

[Slide.]

Now the FDA is currently operating off a 1992 interim guidance that indicates that the NDA holder is the entity subject to user fees. It defines a small business to be $10 million annual gross revenue. And it also, in my opinion, reflects pre-implementation concerns of FDA that waivers would be abused--and, understandably. Because user fees would be a major revenue stream for the Agency, the interim guidance reflects the FDA concerns that waivers could be abused by larger companies.

Now I would not be standing here today if I thought for one moment that what I am about to propose to the FDA would in any way benefit large pharmaceutical and biotech companies who can well afford to pay the application, facility, and product user fees.

I'm here on behalf of small U.S. companies

who are willing to develop therapies for very, very small patient populations; and for those small companies who may be even thinking about developing these products in the future.

I'm here on behalf of rare disease patients who still have no hope of any therapy to alleviate symptoms or to present a cure.

[Slide.]

Now, some orphan companies do pay user fees, because no waiver is granted if a NDA holder is a company with more than $10 million in its revenue. The U.S. licensee is evaluated based on its own revenue, the revenue of the NDA holder, and also all affiliates of the NDA holder.

Now, in 1992, I don't think anyone, including NORD, could have predicted that nations around the world would be emulating our orphan drug law, and would be encouraging the development of orphan products in Europe, Taiwan, Australia and other countries. Therefore, it was impossible for Congress or the FDA to know that foreign countries would be seeking approval of their drugs in the

U.S., and would be seeking companies within the U.S. to license their markets and to market their products.

[Slide.]

Going back to 1992, it is our opinion that the Congressional intent of PDUFA is stated as follows by Senator Orrin Hatch and Senator Kennedy: "The Bill sponsors do not intend for the fees authorized under this Act to serve as a disincentive to the research and development of important prescription drug products; nor should the fees impose an undue financial burden on any company."

Now, when Dr. Kessler was asked a question from the Committee regarding whether developers working on orphan drugs for a disease that affects only 60 children, when he was asked this question he replied, "There is no way we would expect them to pay these fees."

[Slide.]

Now I'll give you a real quick case study. There is a rare genetic metabolic disorder called

tyrosinemia Type I. There are less than 100 cases in the United States, and I believe only 500 documented cases worldwide. It presents itself in the first few months of life, with failure to thrive, fever, vomiting, bruising, enlarged liver, and it can lead to acute life-threatening liver failure and death within the first year of life.

There is one orphan drug, and along with this orphan drug and dietary restrictions, it offsets the deficiency, and children live, they thrive and they grow older.

Now, case in point, if you look at these numbers--and I'm assuming, of course, that DayPro has only one fee. I'm making that assumption. I'm not actually sure if it's correct or not. But if you look at the numbers, there are nearly one million patients taking DayPro. The company pays $335,000 in user fees, and the cost to the patients over one year is only 33 cents.

On the other hand, the 65 patients with tyrosinemia Type I, the company pays the same user fees, and the patients end up paying over $5,000

for the particular therapy that they have to take that sustains life.

[Slide.]

Now, what is the impact on orphan drug development? Well, number one, it reduces the incentive to develop orphan drugs for very small patient populations. It reduces funds available for post-marketing studies into more rare diseases. And it reduces funds available for other clinical research into rare diseases.

And we have a solution, which we have presented to the FDA on a number of occasions. It includes any orphan-designated product that does not qualify for complete waiver of product and facility user fees under the current user fee guidance, shall nonetheless be granted a complete waiver of such fees by the FDA if it meets all the following conditions.

Number one, it must be an FDA-designated orphan drug approved by the FDA for the designated indication. Number two, the orphan had U.S. sales in the previous year of less than $25 million for

the active moiety for all indications, dosage forms, strengths for which the drug is approved, as well as for any off-label use.

Now number two, in particular, is to ensure that large companies don't take advantage of this by salami-slicing a particular drug or whatever, and taking advantage of the user fee. Because our proposal is for orphan products and rare diseases specifically, for very, very small populations.

Number three, it meets the current public health requirement of PDUFA waiver standards.

Number four, the company responsible for the user fee for the product applies for the waiver in the manner and timeframe specified by the FDA.

And, finally, the FDA shall accept and act upon the application without regard to whether the company responsible for the payment of the user fee is also the NDA holder.

[Slide.]

In summary, the problem is that the current 1992 guidance is a barrier to innovation

and a disincentive to conduct clinical research on rare diseases. And NORD's solution removes those barriers to innovation, supports discovery research that is so critical to NORD and to the rare disease community.

Thank you.

MS. HENDERSON: Thank you very much.

Our next speaker is Jeannie Ireland. As director of public policy since 2002, Jeanie Ireland leads the Foundation's advocacy efforts aimed at eradicating pediatric AIDS, expanding HIV-AIDS care and treatment globally, and accelerating the discovery of new treatments for other serious and life-threatening pediatric illnesses.

Ms. Ireland brings a unique perspective to these discussions today, because from 1997 through 2001, as minority staff director for the Senate Health and Education Committee's Subcommittee on Children and Families, she advised Senator Chris Dodd on childcare and health issues and, in that role, she was involved in negotiating the Food and

Drug Administration Modernization Act of 1997, and the inclusion of incentives for pediatric drug testing.

Thank you for being here, Jeannie. You're up.

MS. IRELAND: Thank you very much. And thank you for inviting me to participate today.

I very much appreciate the opportunity to share our views on the reauthorization of the Prescription Drug User Fee Act.

[Technical difficulty. Discussion off mike.]

Again, we very much appreciate the opportunity to comment on the PDUFA reauthorization and how PDUFA might be improved.

I'm pleased to offer the perspective of an organization that's been focused on improving patient access to cutting-edge therapies since its inception in 1998. This issue is at the heart of the foundation's mission. In fact, the foundation's creation was sparked by Elizabeth Glaser's outrage over the lack of options for

treating her two HIV-infected children in the early days of the epidemic.

Since that time our work has expanded beyond domestic HIV and AIDS, to a fight against the global pandemic. Currently we're operating programs to prevent mother-to-child transmission of HIV, and to provide care and treatment at over 750 sites in 20 countries.

Our work has also expanded beyond HIV and AIDS to encompass research and advocacy in support of accelerating treatments for a broad range of pediatric conditions through the Glaser Pediatric Research Network, a consortium of five academic medical centers and children's hospitals that conducts multi-center trials on such pediatric conditions as cancer, obesity and osteoporosis.

In keeping with that mission, we have closely followed the implementation of the user fee mechanism, and are pleased to have the opportunity to comment on ways in which we think it might be improved.

On the whole, we've been pleased with the

success of PDUFA in reducing review times and speeding drugs to market. We are concerned, however, that an unfortunate consequence of the law has been to direct attention, resources away from other critical functions at the FDA; namely post-market safety activities.

In essence, the need to meet review timeframes, and the requirement that the FDA's budget not fall below a certain level has had the effect of focusing resources and attention and leadership disproportionately on drug approvals, and away from the safety monitoring of drugs once on the market. We believe that a central issue in the 2007 reauthorization must be how to give the FDA the authority and resources it needs to improve post-market safety.

It's important to state that we do not believe the answer to improving post-market safety is to return to the days of significant delays in access to new therapies for life-threatening illness. Rather, the solution lies in matching the leadership resources and attention the FDA and

industry have applied over the past decade in speeding treatment to markets, with equal attention to assuring the safety of those products once on the market.

In our view, the solution must include three elements: sufficient FDA authority to conduct critical post-market safety activities; adequate resources; and performance goals as appropriate for those activities.

Under the heading of "sufficient authority," we believe it's important to give the FDA clear, unambiguous authority to require needed post market studies; also to ensure any new authorities are accompanied by flexible enforcement tools; the need for more than the nuclear option of drug withdrawal which only hurts patients; to also ensure that study findings are promptly shared with patients and providers, both through time labeling changes and, for information that doesn't make it onto the label, through a registry of clinical trials.

These new authorities must, of course, be

paired with increased resources. We would suggest an increase in user fees to fund safety activities, including epidemiological studies, high-priority randomized controlled trials, and an increase in support for review of adverse events reports. Obviously, there's precedent for this in the 2002 reauthorization, which allowed some fees to go toward post-market safety activities.

A third element must be attaching performance goals to some of these activities. Simply human nature that deadlines generate attention and focus. Even if additional resources are given to post-approval activities, without deadlines, if they have to compete with pre-approval activities with deadlines, they will lose. Obviously not all activities would be appropriate for setting deadlines, but some would be, including goals for reviewed adverse event reports, and others.

I'd also like to take this opportunity to offer our recommendations for the reauthorization of two pieces of legislation we believe are

essential to ensuring that the benefits of PDUFA, in terms of speeding drugs to market and greater access to new therapies accrued to children. These are the Best Pharmaceuticals for Children Act, and the Pediatric Research Equity Act. Both of these pieces of legislation expire at the same time as PDUFA, and we might expect that they would be considered as part of that reauthorization by Congress.

Like PDUFA, we believe that, in general, these two pieces of legislation are working very well. In fact, I understand that we're very close to, or we've reached, the 100th label change resulting from the Pediatric exclusivity incentives.

There are a few things we would recommend for improving these pieces of legislation. One is to improve the consistency and coordination between BPCA and PREA; the need to address both the overlap between the two and the gaps between the two. For example, currently the requirement in BPCA to make study findings public does not apply to studies

conducted under PREA; nor does the requirement to report adverse events to the Pediatric Advisory Committee. Really no policy rationale why those requirements should not apply to both.

We need to improve the accuracy and speed of labeling changes. We should direct a portion of user fees to fund studies of off-patent drugs, and those on-patent studies that manufacturers have refused to perform. Our experience over the past three years has clearly shown that the existing mechanisms for support that would be helpful for funding these studies are not sufficient. And those were NIH appropriations and drug company or either private-party donations.

We'd also like to remedy what we consider to be the major flaw of the Pediatric Research Equity Act by making permanent the FDA's authority to require pediatric testing of those products clearly intended to be used in children.

So, in conclusion: this reauthorization obviously offers historic opportunity for the FDA and Congress to finally achieve the twin goals of

speeding critical therapies to patients, while also improving the safety and the monitoring of those products post-approval.

I look forward to working with the FDA and Congress on this reauthorization, and hope that we can serve as a resources, and thank you again for the opportunity to speak.

MS. HENDERSON: And thank you for speaking.

And thank you for all of our panelists from this morning. We are just perilously close to being on time. We are about 10 minutes into our lunch time. And rather than penalize your lunch, we will just reconvene here at 1:10 this afternoon.

Thank you all very much.

[Off the record.]

MS. HENDERSON: Back on the record.

Okay, we'll ask our audience to come in and take their seats, and we will get started for the afternoon.

Panel IV - Presentations by Consumer Groups

MS. HENDERSON: Our first panel for this afternoon will be a panel of presentations by

consumer groups. And we are joined to today by William Vaughan, Alison Rein, Arthur Levin, and Diana Zuckerman. And we're going to start with Mr. Vaughan.

Bill Vaughan is currently senior policy analyst in the health sector for Consumer's Union, the nonprofit, independent publisher of Consumer Reports. Starting in 1965 he worked for various members of the House of Representatives' Ways and Means Committee, and he retired in 2001 as Health Subcommittee Staff Director for the minority.

Between 2003 and May 2005, he was Director of Government Relations for Families U.S.A., a national health advocacy organization.

Please join me in welcoming Mr. Vaughan.

MR. VAUGHAN: Thank you very much. And I'm here on behalf of Consumer's Union, publishers of Consumers Reports, which has about seven million subscribers. We're mostly known for evaluating toasters and flat screen TVs. And if you haven't done your holiday shopping, our new issue has some really great ideas.

[Laughter.]

But we also try to help consumers with the

safest, most effective and most reasonably-priced prescription drugs. And we urge the FDA to use the opportunity of PDUFA extension to seek fundamental legislative reforms in the Agency, to continue to bring increased emphasis to safety without slowing approvals, and help the American public understand what medical treatments are truly effective.

As part of this consumer panel, I find I agree with basically everything they're saying, so I won't repeat it all, but will stress a few items, in particular in support of Dr. Tilson, and CERTs, and the need for comparative effectiveness to help the American public what drugs really work and are effective.

And I'd also want to say that I agree with the pre-lunch patients panel. We are in this together. We basically all agree that the FDA needs more resources. We want an FDA that can walk and chew safe gum at the same time, if you will.

Of course the FDA should approve quickly potentially life-saving medicines, at the same time it intensifies research on the long-range impact of those drugs. This should not be an either-or proposition. We're in this together.

I have a full written statement that I hope is before you all. And the FDA asked for an assessment of the overall performance of PDUFA to date. And while there are benefits resulting from the agency getting increased funds to speed review of new life-saving drugs, we believe the overall result of PDUFA has been to undercut the independence and objectivity of the agency.

By shifting resources to speeding drug approval, without a similar increase in drug safety, PDUFA has created a lopsided agenda that, in part, has resulted in the kinds of drug-safety tragedies we've seen in this last several years.

And on the question, "What should be retained or should be changed?" we believe that when PDUFA is extended, collected fees must be decoupled from specific pre- and post-performance

goals that have been rushing the approval of unsafe drugs, and limiting follow-up safety efforts.

We believe a much larger level of income should be collected, since the amounts provided in PDUFA, coupled with impossibly tight Treasury appropriations, have been inadequate to fulfill the overall mission of FDA. And much of the increase should be used by the Agency to improve post-approval monitoring and safety, conduct prior review of marketing materials, and ensure that safety studies are completed to help consumers fully understand the comparative value of approved drugs.

Extending PDUFA is not our first choice for creating an agency that truly serves the public. We believe the Federal agencies that carry out the public's business should be funded by the general treasury to avoid conflicts of interest. As such, we support legislation by Representatives Hinchey, DeLauro and Stupak that would designate that PDUFA fees be deposited into the General Treasury, and that an equal amount transferred to

the FDA as mandatory spending, with no strings attached.

The Bill also includes sections very similar to S. 930 by Senators Grassley and Dodd, that we've endorsed, creating a separate Office of Drug Safety that is appropriately funded, with clearer authority, including civil monetary penalties, to require post-approval safety studies that actually get completed; prior review of DTC adds; immediate adjustment of warning labels; and risk-management programs.

We believe that these types of safety authorities, along with the reforms contained in S. 470 by Senators Dodd and Grassley, that ensure a publicly accessible clinical trial data base would result in a much safer world of prescription drugs, without slowing approval. These measures will take additional resources, but they will fulfill the Agency's mission by ensuring that safety and research have an equal place at the drug approval table.

There's an ancient folk wisdom that he who

pays the piper calls the tune. PDUFA fosters a public notion that FDA is too friendly with the very industry it is supposed to regulate. As has been reported, some in the FDA have referred to the drug industry as "clients." As the September 2002 GAO report on the effect of user fees noted, "The process may have created problems with employee retention and morale."

There is, indeed, a need for more resources, yet there are realistic projections that the Federal debt--Federal debt--will rise $4.6 trillion over the next decade, and that by 2015, our annual deficits will still be running in the $400 to $600 billion a year range before the full impact of the retirement of the baby boomers.

In short, the Federal budget is a disaster, and it's completely unrealistic to expect that if PDUFA expires the Congress will make up the difference out of general revenues. Without PDUFA's resources, it is hard--very hard--to imagine how the FDA would function. Therefore, PDUFA extension is key, but hopefully without

industry-entangling strings.

And industry is best served by the drug-approval and monitoring system that the public trusts. By helping to adequately fund the FDA, industry will be able to begin recovering that vital trust.

As I said, we need the money for post-market safety studies, for aggressive use of new data bases, such as the Medicare drug data base that's coming available, to detect long-term safety problems. Given the long history of marketing violations, the FDA needs the resources to review all marketing materials before they are distributed to providers and the public.

The FDA needs more resources to help bring lower cost safe drugs and devices to market. And we're talking the backlog in generics; the need to find biologic generics that are safe; and then also doing sure safety in the institutional review board Phase I trial process. Bloomberg news reports in the last two weeks, if they're half correct, if they're half accurate, describe a scandal and a

tragedy that threaten individual lives and the very quality of the drug-testing process. And the FDA needs to get on top of what's happening at the IRBs.

We believe that the government should require more scientific, evidence-based studies to help the public understand which drugs are truly effective and safe, and how drugs compare in effectiveness. To slow the unsustainable growth in health costs, we need a comprehensive understanding of what the best course of treatment is, across the variety of treatment options: surgery, medicine, radiation, you name it.

The Medicare Modernization Act provided the beginning of comprehensive comparative effectiveness studies in Section 1013. If this section were adequately funded to undertake a wide array of high-quality trials, the nation could save billions, we think--billions of dollars--in the future by eliminating ineffective medical treatments and medicines.

Unfortunately, the battle in Congress this

year--and it's been a tough one--is whether the amount appropriated would be $15 million or $20 million. Big deal. That's a tiny drop in the bucket, compared to what we need.

And given the long-term Federal fiscal situation discussed earlier, Section 1013's potential will be hard to realize. Therefore, we hope that PDUFA reauthorization will be accompanied by provisions for many, many more Phase IV trials that require new drugs be compared for effectiveness against other drugs. PDUFA resources should be available to help FDA staff ensure that these studies are high quality and completed on time, perhaps in supportive CERTs. These studies, combined with the kind of data that should be available from the Medicare payment data base will finally begin to give us hard information on what works best in the world of health.

One last thing--the gentleman from the Parkinson's group kind of talked about this--is that consumers are involved in the consultation process on PDUFA extension, but only the industry

is involved in the negotiation process, according to that law. And yet in reading the law, there is nothing that would keep the FDA from inviting consumers and patients into that negotiation. And I hope, for the sake of building trust, that the process does become more open.

Thank you very much for your consideration of these recommendations.

MS. HENDERSON: Thank you very much, Mr. Vaughan.

Our next speaker is Alison Rein. Alison Rein is the assistant director of Food and Health Policy at the National Consumers League. Founded in 1899 to bring consumer power to bear on marketplace and workplace issues, NCL is the nation's oldest consumer organization.

Ms. rein designs and coordinates campaigns and other activities around NCL's priority issues, including food safety and nutrition, medication safety, and health care quality. In the last year she has expanded NCL's involvement as a consumer stakeholder in the national discussion about

emerging health technologies.

Ms. Rein?

MS. REIN: Thank you and good afternoon.

On behalf of National Consumers League I'd like to thank you for the invitation to share a consumer-oriented perspective of the Prescription Drug User Fee Act. And I'll skip over a couple sentences that I had inserted about NCL, since they were already stated. But I will add that from the first Pure Food and Drug Law passed in 1906, to the more recent FDA Modernization Act, NCL's been working--often alongside the Agency--to ensure that the public's well being is adequately represented and protected.

Ad so it's in this context that NCL calls on the FDA to seize the upcoming PDUFA reauthorization process as an opportunity to critically examine the impact of the program to date and consider opportunities for enhancement moving forward.

Before going any further, however, I'd like to pause and echo one of the points that was

raised by Bill previously, and that is an observation about the process of comment. There's a growing perception that the FDA has become too intimate with the companies over which it has regulatory authority. And this is view is only exacerbated by the fact that the public has relatively little opportunity for input into the rules governing product review and oversight.

PDUFA provides a clear example of this. When PDUFA was first created, the FDA consulted with Congress and the life sciences industry, leaving health care consumers--arguably the Agency's real customers--out of the loop. The process was made slightly better in the PDUFA III process, as the FDA was charged to also consult with academics and consumers. While a welcome change, consumers are still conspicuously absent from the actual negotiation process. And until consumer interests are directly represented in the final negotiations process, the FDA will not truly serve its real customers.

So, all of that said, I would now like to

turn to the specific question posed for this public meeting. To the first--"What is your assessment of the overall performance of the PDUFA program thus far?--NCL has a somewhat mixed response. In the interest of time I'll just make two quick points to address this question.

First, NCL fully supports the ideal that enhanced drug approval processes benefit everyone. However faster approval does not always mean better. Unfortunately, review time is currently the only performance goal used by the agency to determine success. Throughput, in and of itself, is not a sufficient measure.

Until there is a shift away from the current paradigm of getting drugs to market as quickly as possible, while giving little consideration to product safety in the applied or real-life setting, Americans will continue to e exposed to unnecessary, and often deadly, risks.

I find it a little disturbing: some of the research presented this morning may be taken as proof-positive that PDUFA has had no negative

impact on patient safety. Analysis of the very small sample of actual product withdrawals as the primary endpoint does the issue a tremendous disservice.

Instead of the overly simplistic metric of "product withdrawals," researchers should consider broader measures of patient safety, especially given that, many would argue, that there are many dangerous drugs still on the market, and many patients who have suffered as a consequence.

As a further challenge to this notion, I would simply pose a question: Since when have we been satisfied with the status quo? Should we not be striving to reduce, and not simply just maintain, threats to patient safety?

Second point: NCL believes that the current structure of FDA funding, insufficient in total and with an ever-increasing percentage coming from user fees, forces the Agency into a position of robbing badly needed resources from other important program areas that are vital to preserving and protecting the public's health.

Evidence of this disturbing trend can be seen in chronic staffing deficiencies almost throughout the Agency; persistent inattention to existing programs such as MedWatch; lack of capacity to initiate much needed adverse event monitoring and reporting systems; and reduced food safety inspections--to name just a few.

AS a result, the Agency is in jeopardy of losing the support and confidence of the American people, something it cannot afford to do at this time.

While these are very real and serious issues, revealing some very real problems with the current system, reverting back to Agency funding without PDUFA does not appear to be a viable option. Given the shape of the Federal budget, and our society's increasing reliance on FDA-regulated products, and the need for expanded FDA activity in the area of product safety, it would seem reasonable to actually increase the level of user fees. This would only be acceptable, however, under the conditions that: a) the increase in user

fees does not translate into a diminished total budget allocation from Congress; and b) the user fee funds be applied to the general FDA budget, with no conditions for its use.

While Congress has to date allowed the regulated industries to dictate to FDA how FDA allocates its resources, there is too much at stake to allow this pattern to persist. One potential remedy might involve introduction of a sliding user fee schedule that actually incents drug development in clinical areas identified by the Agency and relevant stakeholders. This type of progressive fee system might do more to more to stimulate innovation in clinical areas of intense need.

So I've already begun to answer part of the second question posed for this public meeting, which is: What aspects of PDUFA should be retained, or what should be changed to further strengthen and improve the program?

NCL could suggest many further modifications to the current PDUFA structure, but I will focus the rest of my comments on one in

particular: the introduction of a new fee for DTCA review.

NCL has long been interested in ensuring that consumers received accurate and useful information about their health care, including information about the safe and effective use of prescription drugs. If DCTA is to remain an integral part of this communications process, then we would propose that product sponsors be assessed a fee as part of their submission of any DTC add, regardless of medium, to the agency.

The revenue derived from the new fee could be used to support a number of currently under-funded agency activities, including, but not limited to: funding of post-market safety studies, as deemed necessary, on a case-by-case basis; expanded use of large data bases to detect safety issues not identified not in the pre-market clinical trial setting; expanded use of secondary data to conduct relative safety and effectiveness analyses; increased expenditure on public information sharing about emerging safety issues,

as well as disease awareness; and hiring of additional staff to review and respond to industry feedback in a timely fashion on all DTC adds pre-deployment.

In addition, FDA should be granted the authority to place a moratorium on all DTC advertising for new drugs deemed by the agency to have inadequate safety information. Based on available safety data, the Agency could be given latitude in determining the appropriate length of the moratorium on a product-by-product basis.

NCL also would support added a third "provisional" status for some new drugs. Such a status would allow for limited exposure of the product to appropriate patients, thereby mitigating the likelihood of inappropriate use and overexposure while additional post-approval safety data collection is ongoing.

In closing I would like to reiterate the point that if FDA budgets continue to shrink at the expense of PDUFA-related programs and review goals, the Agency's ability to satisfy its mission of

protecting the public health will diminish--and with it, the public's remaining trust.

Thank you for your consideration of these comments and recommendation.

MS. HENDERSON: Thank you very much, Ms. rein.

Our next speaker is Art Levin. Mr. Levin is director of the Center for Medical Consumers, a New York City-based nonprofit organization committed to informed consumer and patient health care decision-making, patient safety, evidence-based high-quality medicine, and health care system transparency.

He was recently appointed to the IOM's board on health care services, which has been responsible for overseeing their decade-long effort to improve the quality and safety of America's health care system. No stranger to FDA, Mr. Levin has been a longtime member of our consumer nominating workgroup that recommends consumer representatives for FDA advisory committees; and himself is the consumer member on the Drug Safety

and Risk Management Advisory Committee.

Please join me in welcoming Arthur Levin.

MR. LEVIN: Thank you. A lot of what I'm going to say is going to sound repetitive, but I think it says to all of you that consumer organizations are really on the same page for the most part when it comes to what we think about PDUFA in the past, and what we hope for it in the future.

Like Bill, I'd like to just sort of make a statement of principle that some of us continue to be troubled by this shift that PDUFA represents, from the historic way that the nation's public health activities were funded prior to 1992. Until that time, the FDA's essential public protection programs were funded out of general revenues through the Congressional budget appropriations process. And we think that should be the rule, although we recognize it is not.

That said, there's little doubt in my mind that PDUFA, through its three iterations has substantially achieved what it set out to do: it's

provided the Agency with adequate resources to meet very specific, relatively short review time frames more that 90 percent of the time. Now, we've heard that 50 percent of FDA's resources to do this come form industry. And it's this richness of resources that enables FDA to complete reviews within the specified timeframes, and provide on-demand consultation to the sponsors, aimed at improving the quality of NDAs--a laudable goal and, we've heard today, perhaps a loss-leader for FDA.

Under the law, FDA performance is evaluated on what percent of its application reviews are completed within the prescribed timeframes for priority and standard review. But these are pure management goals, negotiated by industry with FDA, and may have nothing at all to do with a positive effect on the public's health.

We have also not formally determined if the skewing of CDER's resources towards the drug approval process has had unintended consequences on their ability to meet other responsibilities or, indeed, the effect on other centers within the

Agency to meet their responsibilities.

Now, many of us believe that such skewing of resources is at least in part responsible for drug safety surveillance, especially post-market, being a stepchild of CDER. And I know that Steve Galson says that more than 50 percent of the resources within CDER are spent on safety, but I suspect that's taking everything into consideration: pre-, peri- and post-market.

Public and political clamor tends to focus on access to new drugs rather than such mundane public health matters as assuring the safety of radiation-emitting medical technology for canned tuna. Previous FDA briefings have revealed other centers' programs may be sufficiently underfunded and understaffed so as to jeopardize public safety.

Now, over the years advocates have been concerned that a speeded-up review process might present risk rather than benefit to the public. And some FDA review staffers have given credence to this concern in interviews. But there's been a paucity of studies to confirm, deny or appraise the

degree of such risk. One study conducted by FDA staff some years ago argued that PDUFA's speed-up of review times was not a cause for concern. That investigation was prompted by the withdrawal of five drugs in a 12-month period. The researchers concluded that reduced review times under PDUFA were not the cause of this troubling spike in withdrawals.

Yet perhaps the most interesting table in that article, published in JAMA, May 12, 1999, showed that almost 18 million Americans had been exposed to risk from the five drugs prior to their withdrawal. And I guess I would ask: is that level of exposure acceptable?

And as Alison pointed our, the studies we've heard from today also use the metric of withdrawal rates, rather than looking at the population exposure issue.

In this era of experience-based medicine, it seems strange that we've yet to do the study that would tell us whether PDUFA has or has not made an important difference in the lives and

well-being of sick Americans. After all, it's not the numbers of drugs that come to market, it's their quality and their effectiveness and their safety that count.

So, as we continue to discuss reauthorization of PDUFA without the science to support either its continuation or the exact form its continuation should take, I think w need to pause and reflect on the paucity of scientific evidence to determine what the right road to take is.

And another issue, it seems to me that we seem to skirt around is that we're stuck with anecdote and belief that a faster process of review prior to approval is good for the public health. There is simply a lack of evidence that FDA's admittedly pre-PDUFA slow rate of review really caused any excess morbidity and mortality in the United States, when compared with other countries. In fact, although most new drugs are first approved in the U.S.--a turnabout from the pre-PDUFA years--the health status of the populations of

member nations in the now new drug-deprived European Union continues to outrank the U.S.

The notion of U.S. drug lag, borne our of displeasure in certain quarters with the KHA amendments of '62 may be mythical. A study published in 1996 looked at 35 drugs marketed in G-7 countries and Switzerland between 1970 and 1988. And all of these drugs were assessed as having therapeutic significance by experts in this country and in those other countries. The pre-PDUFA, pokey-review FDA approved most of these drugs before they were approved in the U.K. And the U.S. ranked third overall in getting those 35 drugs to market.

Given the political reality of America's national finances, the continued infatuation with collegial, rather than regulatory, relationships between the public and private sectors, and the phoenix-like quality of the drug-lag myth, I, like other speakers here today, assume that PDUFA, warts and all, is likely to be with us for some time to come. And if that's the case, there are critical

concerns I would like to see PDUFA IV address: primarily to strengthen the Agency's ability to protect the public health.

There can be little doubt that concerns about the ability of FDA to conduct safety surveillance once drugs are marketed have grown exponentially over the last two years. Besides obvious deficiencies in surveillance, the Agency also appears to lack necessary authority to take decisive remedial action when the public health is threatened. Such lack of authority relegates the FDA to a negotiating role in regard to risk-management interventions to reduce harm of marketed drugs with demonstrated safety problems, or those sending strong signals of such problems.

I would suggest that if PDUFA IV does nothing else, it must provide sufficient resources to move the Agency's capacity to assure the safety of marketed products from the 20th to the 21st century.

Now, most experts appear to agree that the Agency's current reliance on a passive,

retrospective reporting system dooms it to often fail in spotting serious adverse events associated with drug. MedWatch, the Agency's voluntary reporting system for adverse occurrences related to a drug appears quite capable of unearthing rare and serious events. But because the events are rare, the potential harm to a population of users is relatively small--even though some individuals may suffer a serious or fatal injury.

The passive collecting of voluntarily submitted reports, and the reactive surveillance that follows from such reports is a far from sufficient safety assurance approach. We need to carefully think about how to streamline MedWatch so as to optimize its limited potential, rather an rushing to pour in more resources which will not buy us much in terms of improved safety. An optimized MedWatch, for example, would likely still have lacked the capacity to have picked up the signals of drug-caused increases in risk of heart attach and stroke experienced post-market by users of Vioxx, Bextra and Celebrex.

The supposed second line of defense after the approval and review process, post-market clinical trials, or Phase IV, is unfortunately the

Agency's Maginot line. Consider these numbers published in the February 18, 2005, Federal Register. There were 1,191 open commitments of post-market clinical trials. Of these, 812--68 percent--had not even been initiated; 219, or 18 percent, were ongoing; and only 143, or 12 percent, had been completed with a final report submitted.

But FDA would have to be granted substantial new authority to force sponsor compliance with study commitments, something Congress may not be willing to do. Without such a grant of additional authority, post-marketing studies may never become a reliable mechanism for surveillance of drug safety post-market. And it's important to acknowledge that clinical studies are complex and costly, and that may limit their utility, as well.

What is most needed is a shift from reliance on a passive, reactive system, to one

which is active and proactive. And this would involve using large administrative data bases, where drug use and clinical history of individual patients can be easily linked, and real-time monitoring for safety signals is a possibility.

In the public sector these data bases would include the VA and DoD's active-duty and Tri-Care populations. And I'd like to just comment that, despite efforts in 2000 by then Secretary Tommy Thompson to have the FDA, CDC, AHRQ and these other Federal programs share safety data and other data, that still, to my knowledge, is not a fact.

In a few years Medicare Part D will hopefully provide an important data base linking drug use and patient clinical records to be able to mine safety problems, but the program appears headed for a troubled takeoff over enrollment and cost, and may not provide reliable data for safety monitoring for some time.

Large electronic data bases exist in the private sector. For example, Kaiser Permanente has literally spend billions converting six to eight

million subscribers to an ambulatory EMR system that allows a linkage of drug use to clinical histories. While the FDA has recently stuck a toe in these private-sector data base waters, it really requires more of a complete baptismal approach.

The ability to use proactive real-time surveillance systems may also suggest that we need to think about an addition to the current all-or-nothing approval process. Some sort of conditional approval of drugs where there's a reasonable suspicion of safety problems, or a reasonable hypothesis suggestive of safety problems is likely needed. After all, we agree that many safety problems cannot be uncovered in pre-approval trials because of small sample sizes, short treatment durations, and the exclusion of so-called high risk patients. This would move risk management to a strategy that is not retrospective, but one that is prospective, and I think I would call a "limited marketing" approach.

The cost of establishing linkages with large public and private data bases will not be

insignificant, nor will the cost of getting Federal agency data bases to talk to one another. And simply collecting a lot of data is not enough; in fact, it could overwhelm the FDA altogether.

The FDA must be given the resources necessary to update its computers, and the human capacity for real-time trolling of large data bases for safety signals, and have the skilled staff available to drill-down on those signals, where appropriate. This will require significant start-up costs, new hires, and continued training and operational support.

So, my conclusion: if we're going to have a PDUFA IV, it must include sufficient new resources to enable FDA to do meaningful drug safety surveillance using 21st century technology. Now, that said, I recognize the potential for apparent or real conflict of interest between industry and the Agency, when industry money is supporting safety oversight may even be greater and of more concern than when it supports pre-market approval reviews.

I would therefore suggest that we must be careful to design any supplemental user fee program to allocate more money to drug safety so that the

revenue derived is detached from the specific sponsor source. And we've already heard Bill refer to Congressman Hinchey's proposal to do just that.

We need to hear other proposals that would meet the challenge of avoiding potential conflict of interest head on, while providing the resources critical to support a 21st century safety surveillance system. As important as improving FDA's capacity for drug safety surveillance may be, any proposal that does not recognize the potential conflict of interest and attempt to deal with it up front in the public interest is, in my mind, not supportable.

MS. HENDERSON: Thank you very much, Mr. Levin.

Finally, for this consumer advocacy panel is Dr. Diana Zuckerman, the president of the National Research Center for Women and Families, a nonpartisan, nonprofit research and education

organization that works to improve policies and programs that affect the health and safety of women, children and families.

From 1983 to 1995, Dr. Zuckerman worked as a staffer in both the House and the U.S. Senate, working for the House subcommittee that has oversight jurisdiction over the Food and Drug Administration. In 1995, Dr. Zuckerman served as a senior policy advisor in the White House, working for the First Lady and the Office of Science and Technology Policy.

Since 1996, she has served in leadership positions at nonprofit organizations, and has been president of the National Research Center for Women and Families since 1999.

Please join me in welcoming Dr. Zuckerman.

DR. ZUCKERMAN: Thanks very much.

I'm delighted to be here, and to be with my distinguished colleagues. And let me just say that it doesn't always happen that different consumer groups with different perspectives are in so much agreement, but in this case we are.

I'm going to go in a slightly different direction, however, in my presentation just to talk about the reality of who are using the drugs that

are being approved, and why it's so crucial that PDUFA really focus on safety issues prior to approval as well as post-market; and how important it is that, at the same time, standards are being maintained and criteria are being met for approval deadlines, that the safeguards that are so essential to FDA's appropriate functioning and mandate also be kept.

[Slide.]

These are the healthy people that are in clinical trials. And, you know, there's a range; there's men, and there's women, and there's some range in age. But basically we're talking about studies that are generally done, clinical trials that are generally focused, on health, well-functioning men and women. And not too many of them either; relatively small numbers. But remember that that is going to translate to a huge number of people taking the drugs that are

approved.

From 1993 to 2003, the number of prescriptions that were purchased increased 70 percent, from 2 billion to 3.4 billion. And at the same time, the U.S. population growth was only 13 percent. So there was a 70 percent increase in drugs, 13 percent increase in population. And when you look at a list of the top 300 prescribed drugs in the United States last year--and I'm talking about prescriptions that were actually dispensed--the top 300 range in numbers from a little over 2 million to over 92 million for the year. So you're talking about huge numbers of people, and a very diverse population that don't look exactly like this.

[Slide.]

African Americans, obviously, are using a lot of medications, and yet they are not necessarily included in the clinical trials. Just this past September the FDA came out with a guidance for industry on the collection of race and ethnicity data in clinical trials. But much to our

disappointment, that guidance only talks about the categories of race and ethnicity, and to make sure that they're consistent with other categories used throughout HHS. It doesn't actually require the companies to include any African-Americans or any Asians or any Hispanics.

And so you have a situation where clinical trials are taking place that do not have to include some of the major ethnic groups in the country. And the populations in these clinical trials do not reflect the diversity of our country. And that's important, because although we know, as educated people, that race is a construct that is not necessarily very genetic or biological, we also know that different ethnic and racial groups, as categorized in this country, do tend to respond differently to some medications. And of course you know that, because FDA has responded that by approving a drug specifically for African-Americans. And just this past weekend the New York Times, I think it was, did an article talking, again, about racial differences for

African-Americans in heart disease.

So we know that it's very important that drugs be tested, but there's no requirement that companies do so. And we don't know how often they do so. And when PhRMA puts their statistics out on who's using what drugs, they also don't talk about the racial and ethnic groups that are using them. So there's a lot of unknowns.

But what we do know is that from now on, supposedly, the categories will be appropriate; at least consistent with other HHS agencies. But that doesn't mean that there will be a single African-American, a single Hispanic, a single Asian-American or any other particular group in any of those studies.

[Slide.]

And then there's age. These are, I would call, the "young old" in this photograph. It doesn't really capture the fact that there are millions of Americans that are a lot older than this, that are taking a lot of medications. And they're taking a lot of them all at once.

My 88-year-old dad is taking about 10 different medications in the morning, and eight different ones at night. What kind of data are

there that will say to anybody prescribing these medications what's safe for him? And there are a lot of Americans in the same position that he's in: in their 70s, in their 80s, taking medications that they may be metabolizing differently, and medications that were not really testing on people that old, and certainly not on people who are taking many different medications at once.

[Slide.]

And then there's women. Now, I think the FDA has done a better job in making sure that women are included in clinical trials. But a GAO report that came out in 2001 specified that we don't really actually know that much about how many women are in how many of these clinical trials that are being used.

And these are all the kinds of standards that should be part of PDUFA to make sure that drugs are being tested on the people who will take

them, and to make sure that they're safe and effective for the people who will take them.

[Slide.]

And then there's age. There are young women, there are kids. There are more kids. There are our kids.

And we know that kids are taking a lot of medications. There was an article just recently about how many kids are now taking sleeping pills; Ambien being one of them. Ambien's also an extremely popular drug taken by people over the age of 50. I prefer not to think of those as "old" people, since I myself am over 50. But, let's face it: people over 50 might react differently; certainly people over 60 might react differently to a drug. Kids under 18 might react differently to a drug. They are taking these drugs. And we actually know relatively little about what's going to happen to them.

[Slide.]

So, when you think about the diversity of the people taking drugs who are or are not

necessarily in the clinical trials that the drugs are studied on, I think it's really important that we just use this as one specific example of how we need to make sure that the standards being held to are not just the speed with which a drug is approved, but the safeguards to make sure that it's tested for safety and efficacy, not just on these people, but all the people who are going to take them.

Thank you.

MS. HENDERSON: Thank you very much, Dr. Zuckerman.

And thank you to this panel.

Panel V - Presentations by Industry Groups

MS. HENDERSON: We'll move on to our next panel, which are the industry groups, and I will ask them to come forward: Alison Lawton, Bruce Burlington, and Mary Gustafson. And here they come.

And as they get settled, in the interest of time, I'll start with Alison Lawton's introduction.

Alison is senior vice president of Global Regulatory Affairs and Corporate Quality Systems, and a corporate officer, for Genzyme Corporation,

where she is responsible for all Genzyme products. Genzyme's diverse product portfolio means that she is currently responsible, globally, for biotechnology products including recombinant proteins, monoclonal antibodies, gene therapy, cell therapies, as well as pharmaceuticals, IVDs, combination products, and a range of device products.

Please join me in welcoming Alison Lawton.

MS. LAWTON: Thank you. Can I just make sure everybody can here me at the back. Yes?

So, on behalf of the biotechnology industry organization I want to say thank you for this opportunity to comment on the effectiveness of PDUFA program, and to support its continuation.

BIO membership includes many small start-up companies in early stages of product development which have not yet applied for FDA approval; biotechnology companies whose exclusive

focus is on the development of biological products; and large well-established pharmaceutical companies that simultaneously pursue the research and development of small-molecule conventional drug products and complex biological products.

BIO member companies are committed to developing innovative therapies focused on unmet medical need. And member companies, regardless of their size or situation, all recognize the crucial importance of three general PDUFA goals: expediting the review and approval of new therapies; reducing the length of time it takes to bring an innovative concept through the development process to completion as an approved, safe and effective therapy; and making FDA processes and outcomes transparent and predictable to industry and to the public.

BIO believes that the overarching aim of the PDUFA program should continue to be measurable improvement in access for patients to new life-saving and life-altering medicines.

In large measure, the goals of PDUFA are

being achieved. The statistics are clear: post-PDUFA, U.S. patients are the first in the world to have access to new products, as a percentage of total drug launches by country. And you saw some of that data this morning.

Prescription drug user fees, added to a sound base of appropriations for FDA, have provided the additional resources needed by the agency to reduce the backlog of applications that led to the so-called drug lag in existence before the enactment of PDUFA. PDUFA fees are intended to provide FDA with the ability to increase its review capacity, including medical and scientific expertise so the agency can become more efficient without reducing its commitment to the highest standards of review.

The intention of Congress in enacting PDUFA initially, and in renewing it twice, was, and we believe remains, that this program significantly contributes to and supports the safety and efficacy of prescription drug and biological products.

PDUFA does this by providing FDA the resources it needs to continue to make sound, scientific, medical and regulatory decisions.

The PDUFA program both supports new medical innovation and is, itself, an innovation. Since its inception, PDUFA has helped to speed more than 220 new cutting-edge drugs and biologics sponsored by BIO member companies. And these products have made a difference to patient lives. Indeed, the PDUFA program is considered highly innovative in itself, and in 1997 received the prestigious "Innovations in American Government Award" sponsored by the Ford Foundation and Harvard University's John F. Kennedy School of Government.

PDUFA has earned this high praised as a mechanism for consistent, multi-year FDA funding needed to conduct more predictable, empirically-based product reviews.

We strongly support the renewal of PDUFA in 2007 when the current program expires, and believe that maintaining level funding will allow the successful continuation of the program.

As we examine the data being collecting during the course of the present program, we hope to achieve a better understanding of causes and

possible solutions that will show that modest programmatic changes may contribute to even greater success.

We have some specific comments in three areas: safety, information technology, and performance goals.

So let me start with safety. BIO believes it's important to recognize that safety is an integral and paramount part of companies' considerations during research and development, and of FDA's deliberations during its application review. Indeed, FDA has stated that it spends half of its effort and resources during the course of a review in considering the product safety profile, and determining whether limitations on use or specific content in the labeling are needed to ensure consumer safety.

Because PDUFA funds were specifically designed to be allocated to activities related to

application review, they clearly should be used by FDA for pre-market safety-related activities. During the most Congressional renewal of PDUFA, Congress, FDA and companies agreed that user fee resources should also be allocated to safety-related activities that occur in the early post-market period, when a great deal of safety information may be obtained as products transition from use in a relatively small number of patients enrolled in clinical studies, to use by many more people. This new PDUFA allocation, $63 million, provides for additional personnel, data base enhancements, funding of outside reviews, etcetera, focused particularly on the so-called "peri-approval period," that is, the first several years the product is on the market.

BIO does not agree with suggestions that PDUFA has contributed to a lowering of FDA safety review standards, or reduction in product safety, or that safety has taken a back seat to speed. PDUFA fees are, in fact, applied directly to safety

evaluation, both in the pre- and post-market stages. And you heard this morning that there was a study from the Tufts Center, a study of drug development, which demonstrated that there's no evidence of correlation between the length of the application review and product withdrawals.

As PDUFA moves towards renewal, we want to focus on safety-related areas to determine if and how improvements can be made. And we look forward to discussing these in more detail as the process evolves.

BIO would like to see some emphasis placed on the greater efficiency, consistency, and predictability in the process of evaluating trade names. Trade name evaluation is an important aspect of safety, in that it helps minimize medication errors. Currently, we believe trade name review is not conducted in a timely manner, and consistent procedures do not seem to be in place for this aspect of application review. This is a significant issue for BIO member companies, and we believe that statutory changes are not

necessary to make these improvements, so BIO looks forward to working with FDA to expeditiously improve the evaluation of trade names.

I'd now like to move on to information technology. Implementation of data and document standards is generally embraced by the biotechnology industry. During the course of PDUFA III there have been promising steps toward establishing the base architecture for paperless submissions. This goad is critically important, and we look forward to its achievement.

However, FDA appears to struggle with the existence of multiple external standard groups, and numerous IT groups within the FDA. We encourage the agency to better consolidate and coordinate IT activities related to electronic submissions. We also encourage, and will continue to work with FDA to achieve this: better communication of IT initiatives and implementation.

In addition, it's crucial for companies to have sufficient advance notice of changes and of implementation of new requirements to be able to

comply with the Agency IT changes. That is not currently happening uniformly.

So, finally, let me talk about performance goals. In general, we believe appropriate goals for review performance are in place and should be retained, but we want to highlight several matters.

Statistics currently available, including FDA's annual performance reports indicate that median approval times are not changing, notwithstanding the fact that, overall, PDUFA spending on application review has continued to increase annually. Moreover, the current median time to approval is longer than the comparable in 1999. It would be helpful for FDA to provide additional details regarding this issue and develop a clearer understanding of whether and how use of PDUFA funds are contributing to this apparent slippage.

One of Bio's key priorities in the most recent PDUFA renewal was to achieve an understanding of differences in product approval times between biological products and drug

products, among review divisions, and between the Center for Drug Evaluation Research and the Center for Biologics Evaluation and Research. In particular, FDA used PDUFA resources to fund several studies to shed light on this, including studies of first-cycle review, the results of which will be helpful in understanding the time to approval. And we look forward to getting more data on these ongoing studies.

A critical issue identified in PDUFA renewal discussion was that of inconsistencies between and among reviewers and divisions. One goal of PDUFA III was the development and implementation of good review management principles. FDA has developed and disseminated this GRMP guidance, and has begun training the reviewers in both CDER and CBER regarding these best practices. This was an important achievement. However, sustained and continued commitment to observing the principles articulated in the guidance is critical to success. This includes continued dedication to performance and

communication goals, training, and implementation of GRMPs.

While progress is being made, two areas represent opportunities for further examination and possible enhancement: labeling, and post-market commitment negotiations. Again, we feel that changes in the law are not necessary to achieve these efficiencies. And again we look forward to continuing our productive dialogue on these issues.

Another PDUFA III activity predicted to be a potential route to enhanced communication and reduced review time was the establishment of two continuous market application pilot programs. These programs have been implemented and are currently being evaluated by FDA. We look forward to learning from FDA how the CMA programs were implemented and used, and the FDA's views on these programs. We will also do our own assessment of the programs, although preliminary assessments appear to indicate that these programs were not used as often as we might have anticipated. And, in addition, it appears that while these programs

were worth evaluating on a pilot basis, without compelling data regarding their success, they may not be worth continuing, especially if they have significant impact on FDA resources.

Overall, BIO believes that good progress is being made in meeting PDUFA III performance goals. As FDA itself has acknowledged, however, there has been little success with respect to meeting goals for management of meetings and other communications with applicants. Because this is an area of great importance to BIO member companies, who view good communication with FDA as their lifeline to predictability and success, we hope to continue to work with FDA to realize the meetings management goals established in PDUFA II.

We're aware that over the last several years FDA appropriations for drug and biologics review have remained flat when adjusted for inflation. Consequently the Agency has struggled to keep up with its review activities with the multiple other tasks with which it's charged. We will continue to urge Congress to ensure adequate

FDA appropriations.

So, in conclusion, BIO believes that reductions in overall product development time and in FDA review time both are critical factors in improving access to medicines. PDUFA is key to this goal.

The program should be reauthorized in a timely manner and not redesigned with reforms unrelated to PDUFA's goals. User fees at current levels should continue to provide reliable additive resources for human drug and biologic review, while FDA works towards realizing the goals established in PDUFA III, with minor programmatic improvements.

I want to emphasize again Bio's view on the program is that it has been highly successful, and is a direct contributor to increased patient access to life-saving, breakthrough therapies, and we look forward to working with you in the coming months.

Thank you again for the opportunity to speak on behalf of Bio.

MS. HENDERSON: Thank you very much, Ms.

Lawton.

Next on this panel is Dr. Bruce Burlington. Dr. Burlington is executive vice president for Quality, Regulatory, Safety, Compliance and Audit at Wyeth Pharmaceuticals, located in Collegeville, Pennsylvania. In this position, he has responsibility for the regulatory affairs, safety surveillance, quality operations, compliance operations and audit departments, all on a worldwide basis.

Please join me in welcoming Dr. Burlington.

DR. BURLINGTON: Thank you very much. I'm pleased to present a statement on behalf of the Pharmaceutical Research and Manufacturers Association.

When Congress in 1992 passed the Prescription Drug User Fee Act, it was a reasonable means for improving the review of new drugs. The average review time at that point had increased to nearly 34 months. And, as Dr. David Kessler stated, this was attributed largely to a lack of

trained reviewers to undertake the work for the Agency. When the law was enacted it was established on two critical concepts. One of them is that the fees paid by the industry were to support additional reviews in the Food and Drug Administration; that only the timing of new drug reviews would be part of the metrics and goals. There was no assumption about the approvability of applications, individually or in general. There was a commitment by Dr. Kessler that the Agency would use these resources to produce faster reviews.

When the law was enacted and signed by George Herbert Walker Bush, the user fees were clearly to augment, and not replace, FDA's base appropriations. They are not a new tax. They are specified fees for improving drug-review services, and cannot be used to fund other obligations and functions.

There were, at the time of enactment, bedrock safeguards to assure user fees were additive to FDA's base budget, and that the fees

were dedicated to the review of new drugs and related activities.

It is critical that Congress provide adequate base funding for non-PDUFA FDA activities in order to make the system work. These are reasonable and sound principles, and they must be maintained.

In addition, the framers of PDUFA established accountability to Congress for FDA performance as a basis for continuing the program. The goals and results under the PDUFA and its re-enactment have been transparent to all stakeholders; and FDA's performance has been excellent. They have consistently met PDUFA goals.

Further, as we have heard today, innovative medicines are routinely approved and launched and available to U.S. patients and consumers before they are available elsewhere in the world.

I won't dwell on the various elements of the re-enactment, the FDAMA or subsequent re-enactment of the legislation, but I would

note--and this has already been addressed by my colleague from Bio--that funding for information technology initiatives had been part of the last two re-enactments, as well as the introduction of funding for post-market surveillance related to application review, and in the peri-application period.

As user fees near the end of the third five-year term, it's important that we consider the value that the program has brought; value to both society and the Food and Drug Administration, as well as the industry. We have realized the benefits envisioned when Congress enacted PDUFA in 1992. The FDA has increased the number of review staff. They have augmented post-market safety surveillance activities, and they have improved internal information technology capacity.

The pharmaceutical companies have been able to bring drugs more rapidly, and with more consistency, through the regulatory process to consumers. And patients have received faster access to innovative medicines, improving their

health and quality of life.

This has been accomplished while the extent of safety data to support an approval has continued to grow, and while maintaining FDA's high quality standards as the gold-standard regulatory agency throughout the world.

As we consider PDUFA IV, it is important we bear in bind that accountability for goals and measurement of performance against these goals continues to be an important aspect of the program. Goal setting enhances performance. Every good manager knows: you get what you measure.

Today, in industry, we must with increasing stringency account for the way we use resources. There is a general constraint on the availability of new money in R&D across industry, as industry looks at the change in the payment model for pharmaceutical products. Many companies have taken steps to reduce their costs and overhead. It is not a time when there is a luxury of money which can be transferred from the research on pharmaceutical products to new applications.

Therefore, one of our considerations should be to minimize the work necessary to document achievements, and not reduce goal setting.

FDA can maintain a performance-based environment and collect data on their performance much more efficiently than they have in the past. Electronic submission requirement makes it easier for electronic record-keeping, and offers the prospect of gained efficiency. Implicit in these efficiencies would be savings in manpower and funds so FDA can reallocate them to other activities.

In terms of data analysis for the information collected under the PDUFA program to date, FDA has developed an extensive data base. Analysis of this should assist the FDA in implementing their quality systems program, yielding greater consistency of reviews for the industry. Further the analysis of first-cycle reviews and multi-cycle reviews should provide important lessons, both to the Agency and to the companies, about how to better conduct their research and development of products, and bring

more mature applications to the agency.

Under risk management, it is important that we continue the work begun in PDUFA III on risk management, with Agency working with the companies to bring the best benefit to risk ratio to consumers; the cornerstone of the new approach to drug safety issues used by both FDA and the industry, so that the approval of critical new medicines is not unduly delayed.

The Pharmaceutical Research and Manufacturers Association supports the re-enactment of the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act, both due for renewal in 2007, as well. They have worked as intended.

The number of new pediatric studies has increased markedly: 251 have been initiated by company proposals; and 93--and we've heard this morning, around 100--drug labels have been updated with significant new pediatric information.

The PDUFA legislation has worked and should be reauthorized. Positive results of PDUFA

cannot continue without stakeholder commitment to a user fee program, full Congressional support of base appropriations. And I would note that Dr. Woodcock earlier this morning showed us that the appropriated base has eroded steadily over the last 12 years. This needs to be fixed.

Further improvements of the review process by FDA scientists are also an important element of PDUFA renewal. Patients, the public, as well as industry, need an unambiguous, consistent and predictable set of standards in the development of drugs for the future. FDA needs the assurance of adequate staffing and resources so that drugs now in development, and NDAs currently before the agency can be reviewed in a timely way.

Without continuation of PDUFA, opportunities for continued improvements in drug safety programs will be limited. Without a continuous assurance of PDUFA goals there is an uncertain future for the scientific breakthroughs that occur each day, and industry's work to turn them into pharmaceutical products for patients in

need.

Thank you.

MS. HENDERSON: Thank you, Dr. Burlington.

Last on the industry panel is Mary Gustafson, senior director for Global Regulatory Policy at the Plasma Protein Therapeutics Association. Prior to joining PPTA, Ms. Gustafson served as senior director of Regulatory Affairs at Nabi Biopharmaceuticals in Boca Raton, Florida, and in regulatory positions at the FDA. While at FDA, she directed the Division of Blood Applications in the Office of Blood Research and Review in the Center for Biologics, as well as holding earlier positions in biologics compliance and product certification.

Ms. Gustafson?

MS. GUSTAFSON: Thank you, Debbie. I do have slides.

PPTA is pleased to be part of today's program, and thanks FDA for initiating a public process for the important work of reauthorizing the Prescription Drug User Fee Act.

[Slide.]

PPTA is the international trade association and standards-setting organization for

the world's major producers of plasma-derived and recombinant analog therapies. These therapies are subject to prescription drug user fees, and include blood-clotting therapies, immunoglobulins, therapies for alpha-1 antitrypsin deficiency, and albumin. Our members also provide source plasma, which is the primary source material for the manufacture of plasma for plasma-derived protein therapies. Source plasma is not subject to user fees, and must be regulated using allocated funds.

[Slide.]

The companies pictured on this slide represent the PPTA member companies that are subject to user fees for the therapies they produce. As others have mentioned, our companies viewed the Prescription Drug User Fee Act of 1992, and its two previous reauthorizations, as benefitting the industry and patients who receive our therapies. Thanks to the user fee program,

life-saving therapies have been introduced to the market. The benefits of reducing time-to-market for these therapies cannot be overstated.

[Slide.]

PPTA member companies, including those not subject to user fees, are regulated by the Center for Biologics Evaluation and Research. The products produced by our companies are reviewed in the Office of Blood Research and Review.

PPTA is concerned that CBER, and particularly the Office of Blood, is resourced adequately to perform all regulatory functions. CBER is unique in that it operates under both PDUFA and the Medical Device User Fee Program, MDUFMA, in addition to having significant programs that are not supplemented by user fees. And note: I said "programs," not functions or activities within a funded program.

It is very important to our companies that user fees in both programs are used appropriately, including tracing and accountability; but that the non-user fee programs are also adequately resourced

with allocated funds to cover the full extent of the Office of Blood and CBER's needs.

Believe it or not, these programs are interactive for part of our industry. Manufacturers subject to PDUFA are dependent on reviews and policies affecting non-PDUFA products, and are dependent on test kits and other devices subject to MDUFMA.

While the user fee programs were always intended to be supplemental, we have concerns that the base allocations have eroded. It is important to maintain strong programs within the Office of Blood and CBER, whether under a user fee program or not. Therefore, we encourage Congress to provide adequate funding to CBER, and all of FDA, with user fees truly being supplemental.

PPTA was not part of the negotiations for PDUFA III. However PPTA members voiced a need for faster and more predictable lot release. CBER listened and developed internal lot-release standards independent of user fees. It is that responsiveness that we hope CBER will continue to

be able to support, whether it's a funded activity or not. In order to allow this responsiveness, CBER, and FDA in general, needs to be adequately funded.

[Slide.]

While review of the performance of the Office of Blood and CBER is favorable, we do feel that the program could be improved by increasing the transparency in reviews. While we know that as a commitment to PDUFA III CBER and CDER published a guidance document entitled "Guidance for Review Staff and Industry: Good Review Management Principles for PDUFA Products," this document provides timetables for various steps in the review process. We also acknowledge that the mid-cycle review and subsequent communication has improved the predictability of the review.

However, we still feel the process can be improved by adding a real-time tracking feature, ideally electronic, that would provide tracking information in real time that could be accessed by the manufacturer. We consider that such a system

would increase the predictability of approval more than has been available now.

Being able to predict when a product will be approved is of great importance. It allows manufacturers to plan for launch of a product that may have substantial improvements over existing products. It allows the manufacturer to control inventories, schedule production runs, and plan for release of newly approved product without delay.

There is much focus today on safety in the first months and years after a new or changed product enters the market. We share these concerns. If enhanced surveillance is to be considered under the user fee program beyond what was funded under PDUFA III, we would advocate that any post-market surveillance program, or program to standardize post-market studies undertaken as Phase IV studies, be determined on an interactive basis between FDA, industry and stakeholders. Patients of our therapies are generally lifelong users, with valuable knowledge based on history and experience.

[Slide.]

As part of getting ready for PDUFA IV negotiations, PPTA borrowed a survey tool developed by BIO. We were able to get responses before this

meeting, perhaps because all of our member's logos fit on one slide.

Please consider these comments to be a snapshot in time, not a statistical sample of the entire PDUFA-funded industry, nor even consensus among our members at this time. But presenting them today may provide a hint of where a subset of the industry is on these issues.

The survey was divided into two questionnaires: the first questionnaire focused on the pilot programs initiated under PDUFA III. The pilots were associated with the continuous marketing application. The pilots were to test whether early review of selected applications and additional feedback and advice to sponsors during drug development will shorten drug development and review times. The first pilot addressed the rolling review of selected applications; the second, with increased accessibility to Agency

reviewers during the development and review process.

As you can see, none of our members participated in these pilots for various reasons. Both of these pilots were designed for products with fast-track designation, and products at certain stages in the development. There were no products available for the first pilot.

As to the second, our members viewed the reviewer access adequate as is.

As to whether these programs should be continued, there was a mixed response.

[Slide.]

Also included in the second questionnaire was a question about the special protocol assessment. No one had used it to date; again, a mixed review on its worth.

[Slide.]

Participants in the survey were asked whether they reviewed the performance on changes to an approved application designed as CBE-30s to be adequate: specifically, were CBE-30s classified as

pre-market approval applications after the 30-day time frame?

For the most part, CBER got good marks on this, however, some viewed it time to re-evaluate the classification criteria used within each category based on the experience gleaned in the near decade since the tiered changes-to-be-reported categories were codified.

[Slide.]

In summary, PPTA member companies consider the Prescription Drug User Fee Program to be successful, and should be reauthorized. In the initial survey of member companies in preparation for renegotiating PDUFA, companies view the current goals to be adequate, with a few enhancements. Companies reported mixed reactions to some of the PDUFA III goals.

PPTA member companies are concerned that CBER, who regulates our products, is adequately funded to perform its functions in administering PDUFA and MDUFMA, and support its many non-user fee programs.

In terms of priorities, PPTA member companies desire a more transparent review process, and input and interaction in the design of any

enhanced funded pre-marketing program.

Thank you.

MS. HENDERSON: Thank you very much, Mary. And thanks to our entire industry panel.

We will now take a 15-minute break, after which will have a panel of presentations by health professional groups, followed by an open public comment period.

So please return to your seats at 2:45.

[Off the record.]

MS. HENDERSON: Back on the record.

Panel VI - Presentation by Health Professional Groups

MS. HENDERSON: I'm very pleased to welcome our next panel, which is the panel on health care professionals.

Our first speaker is Carol Redding Flamm, who is senior medical director in the Office of Clinical Affairs at the Blue Cross and Blue Shield

Association. Dr. Flamm's responsibilities at the association include improving the safety and health outcomes of episodes of care experienced by Blue Cross and Blue Shield plan members through collaboration with the providers to whom their care is entrusted. She also manages the many quality-based Blue Cross and Blue Shield Association Network Initiatives.

Prior to work at the Association, Dr. Flamm was an instructor of radiology at Harvard Medical School, and also served as an associate in radiology in Beth Israel Hospital in Boston, Massachusetts. She received her medical degree from the University of Pennsylvania, and holds a master's degree in public health from Harvard.

So we are very pleased today to have Dr. Flamm.

DR. FLAMM: Thank you. I'm here on behalf of the Blue Cross/Blue Shield Association, representing the 39 independent plans ensuring more than 93 million people, nearly one in three Americans. And we thank you for this opportunity

to comment on PDUFA reauthorization.

In our brief comments today we're going to be looking at PDUFA's impact on safety primarily, and offering some recommendations to further strengthen and improve PDUFA.

In 2001, Blue Cross/Blue Shield Association recommended expanding PDUFA user fees, and increasing activities to include post-marketing surveillance. And with the reauthorization in 2002, PDUFA was expanded to include drug safety functions, specifically looking at monitoring adverse events, and disclosing Phase IV studies.

[Slide.]

In keeping with some of the comments that others have made today, we would also emphasize that safety should be integrated into delivering new drugs. There is the concern that faster drug approvals mean potential side effects and interactions are often not known at the time of market entry. This is important because adverse drug events cause 770,000 injuries and deaths each year, and we are firm in our belief that voluntary

reporting of adverse event rates is not adequate.

[Slide.]

Looking at where the money is spent in CDER's budget, 47 percent of CDER's budget comes from PDUFA fees. And the Office of Drug Safety gets 6 percent of CDER's budget.

The cross horizontal marks are PDUFA fees, and these are appropriation fees, and this down here is the Office of Drug Safety. So you can see that about 33 percent of the Office of Drug Safety fees come from PDUFA fees.

[Slide.]

In terms of Blue Cross/Blue Shield's recommendations for safety, we would suggest keeping the emphasis on PDUFA's drug safety functions, and devoting additional PDUFA funds to the Office of Drug Safety. For example, shifting the relative proportion of PDUFA fees that CDER has in its budget from 47 percent, shifting the Drug Safety proportion from 33 percent up to 47 percent, and keeping that parallel would be one recommendation that would provide $7 million

additional dollars.

[Slide.]

We would also recommend to further strengthen and improve PDUFA in two ways by offering that PDUFA increase its role ensuring comparative information, as was mentioned by several other speakers earlier today. And we would suggest that it include monitoring of direct-to-consumer advertising activities and compliance.

[Slide.]

There is a lack of comparative information in what consumers have available when drugs are available on the market. Consumers need information on relative costs, benefits and risks of new drugs that replace existing therapies, and the FDA should require manufacturers to provide this comparative information. Just as two examples, common conditions, asthma and diabetes, there are gaps in the knowledge that is necessary for patients to make decisions.

More information about the relative value

of various asthma treatment, in terms of symptom-free days, decrease in work days loss, and any decrease in the use of in-patient services--things that matter to patients--would be very important.

And in diabetes, little is known about the effectiveness of new diabetes drugs compared to older therapies, in terms of their ability to reduce the long-term morbidity of that disease.

[Slide.]

In terms of direct-to-consumer advertising oversight, lots of money is spent on this type of advertising: $2.7 billion in 2001; $3.2 billion in 2003. And today's DTCA spending is estimated to be $4.2 billion.

[Slide.]

The FDA's Division of Drug Marketing, Advertising and Communications--DDMAC--is responsible for reviewing DTCA. This division employs 39 people, of which five are dedicated to reviewing DTCA; and the total budget is $5.5 million. We would suggest that you consider

extending PDUFA funding to DTCA review, as well.

[Slide.]

In summary, PDUFA has a very important role to play in improving safety, and our recommendations include increasing the percentage of PDUFA fees that should go to the Office of Drug Safety for post-marketing activities. PDUFA should ensure consumers get comparative information; and that PDUFA should be expanded to direct-to-consumer advertising monitoring as well.

Thank you.

MS. HENDERSON: Thank you very much, Dr. Flamm.

Our next speaker is Judith A. Cahill. As executive director of the Academy of Managed Care Pharmacy, Judy Cahill has responsibility for policy creation and implementation, administrative operations, and overall staff leadership of the Academy of Managed Care Pharmacy. The Academy is a professional society wit over 4,800 members nationwide which is dedicated to the continuing professional development of pharmacists and other

health care practitioners engaged in the practice of pharmacy in managed care settings.

Ms. Cahill holds a bachelor of arts degree from LeMoyne College, a master of arts degree from the University of Cincinnati, and certification as an employee benefits specialist from the Wharton School of Business.

Take it away, Judy Cahill.

MS. CAHILL: Thank you very much. On behalf of the Academy of Managed Care Pharmacy I'm please to be here today, and to have the opportunity to present our views on at least one aspect of PDUFA renewal.

Let me explain to you the basis from which I speak: and that is from the organization that I represent, the Academy of Managed Care Pharmacy.

[Slide.]

We are a professional society for pharmacists who have chosen to practice their profession by the application of managed care principles. We have individual pharmacists and health care practitioners in our membership who are

dedicated to getting the appropriate drug to the appropriate person in a way that is affordable and accessible.

We apply those managed care principles in that endeavor in order to ensure that the quality of care that patients need from managed care organizations are extended to them.

And it is in that light that we are very concerned about the post-market surveillance activities that the agency can engage in. We have approximately 4,800 members nationwide. They in turn, because of the system they work for, service 200 million Americans.

[Slide.]

I won't waste time on this because we've heard it several times today, about the aspects of PDUFA 2002 that did provide real benefits to the whole area of getting appropriate medicines to patients. But I do want to bring to your attention the last point on this slide, and that is that the 2002 renewal did little to address post-market surveillance. There were hours that were set aside

for peri-surveillance, but those were only for the early years of usage of a drug in the marketplace. And we believe, within the Academy, that there needs to be more thorough, more comprehensive post-market surveillance.

Because we are firmly dedicated to the idea that when you look at populations you're able to draw conclusions that are not obvious from smaller studies, and that are now obvious by anecdotal, one-on-one patient encounters with drugs, there needs to be a thorough ongoing collection and review of data related to problems associated with a drug's use to determine if the drug can continue to be marketed with its original restrictions; if those marketing requirements need to be changed; or if the drug indeed needs to be removed from the marketplace for the safety of the population.

[Slide.]

We support epidemiological studies that demonstrate the safety and effectiveness of medications when prescribed in the real world of

the general population. Although randomized clinical trials can be used, and can be effective in rather narrow parameters, it is because of those narrow parameters that we favor the epidemiological studies. There you can look at patients who are using the drug, who have co-morbidities, who are taking multiple medications, and who are being prescribed drugs that are for not-indicated uses.

Because of the variety that epidemiological studies offer in the general population, we believe they are a better indicator of what happens when a drug moves to post-approval status.

[Slide.]

We believe there's a shared responsibility for post-market surveillance. And I would put before you that there are three major players when it comes to post-market surveillance. There is the manufacturing community. There is the practitioner community. And there is the FDA.

[Slide.]

Manufacturers of medications have the same

obligation as manufacturers of any product that is put before the consumer, and that is: responsibility over the life-cycle of the drug. And we would suggest that post-market surveillance is an area of manufacturer responsibility that--as we have heard before, earlier today--is not often completed. We would encourage that that change. Practitioners have an obligation to report adverse drug events. And we've heard again today that that happens rarely. When it does happen, the Agency is not properly staffed or funded to be able to follow through on many of those ADRs that are reported.

[Slide.]

The Agency itself, in its fundamental goal of promoting and protecting the public health by determining a drug or biologic's safety and effectiveness based on clinical research is at the heart of what we are talking about in both pre-, peri-, and post- surveillance. We, of course, know that FDA approval does not mean that a product is risk-free. There is no opportunity to be able to fully, effectively compare risks and benefits of a

given product. But it is in the wisdom of the approval process that we are able to say, with at least some degree of certainty, that the benefits do outweigh the risks. Problems associated with drug use often only appear after several years of use in the general population.

[Slide.]

FDA is in a unique position to aggregate data on what happens to the use of a drug in the general population. Post-market surveillance provides expanded data on what actually are the results of using a medication that can go to educate practitioners on minimizing risks for patients that they are prescribing medications for, and they can go to educating prescribers on the most appropriate use of drugs.

[Slide.]

There are changes that are definitely needed. FDA's authority to monitor a drug after approval is limited. We heard statistics earlier today that only 12 percent of the Phase IV studies that are requested by the Agency are actually

completed. Not a good track record.

FDA needs the authority to enforce the requests that they make for Phase IV studies. The suggestion that was made by a presenter earlier today that those Phase IV studies be the result of collaboration amongst stakeholders of many sorts I think is an excellent idea, and one that, should we be successful in getting funding for post-market surveillance in a meaningful way, will produce the guidelines that we need in order to be effective for the patient populations we serve.

[Slide.]

We want to congratulate CDER on its recent award to managed care organizations with large data bases contracts that will allow those data bases to be mined, to see the interaction of health care encounters, and the medications the patients are on. We believe this will provide a rich trove of information that has not been available before this, and applaud CDER for the action in this area.

[Slide.]

We do see the need for legislative change

with regard to post-market surveillance, and would hope that this would happen prior to PDUFA renewal but, if not, certainly as a part of PDUFA renewal.

The Academy has been on Capitol Hill championing these two specific points, and that is: giving the Agency the authority to require post-market studies, and then funding the Agency to the extent that they will be able to enforce those studies.

I thank you for your time and attention today.

MS. HENDERSON: Thank you very much, Ms. Cahill.

Next on the panel is Susan Winckler. Susan Winckler is the vice president for Policy and Communications, and staff counsel for the American Pharmacists Association, the first established and largest national processional society of pharmacists, headquartered in Washington, D.C.. In that capacity she is responsible for coordinating the association's legislative, regulatory and private-sector advocacy agenda and communication

programs.

Ms. Winckler serves as the primary spokespersons for the association for media interviews, and is the senior lobbyist for the association on Capitol Hill. In 12 years with APHA, she has served the profession in various capacities, including group Director of Policy and Advocacy, and Director of Practice Affairs.

Ms. Winckler is a graduate of the University of Iowa College of Pharmacy, and the Georgetown University Law Center.

Please join me in welcoming Susan Winckler.

MS. WINCKLER: Good afternoon. And on behalf of APHA, thank you for the opportunity to be here this afternoon.

[Slide.]

To provide a baseline of where our comments are coming from, APHA, the American Pharmacists Association, represents pharmacists and all practice settings, whether in the community environment, the hospital, managed care, or any

environment where folks with our education choose to practice.

We have more than 53,000 members, and are particularly interested in today's topic as we consider the FDA processes and the information that's available from those processes as funded by PDUFA, and how it affects the health care system, and how pharmacists help patients make those medications work.

We have two primary comments today: to assess the PDUFA performance; and then to comment about expanding the scope.

[Slide.]

When we look at PDUFA performance and whether we have met the original goals--I think, as you've heard throughout the day, probably have no surprises from this panel--the fee-for-service model kind of set out by PDUFA has yielded more timely and predictable reviews. And for those drugs that meet the approval standards, they are getting to patients faster.

A question I think we must always raise

when we talk about renewal of PDUFA, however, is that PDUFA does not replace the need for appropriations, and the understanding that we must continue to have Federal investment in this essential infrastructure in order for our health care system to continue to function.

We should also continue to have allocation for drug safety post-approval--and that's a piece that I'll talk about as we talk about expanding the scope--and understand, generally--and this hasn't happened with the Agency--but we should always keep an eye on the need for a focus on speed not distracting from our focus on quality. That hasn't yet happened. But likely the best way to keep that from happening is to keep in our minds that we want to make sure that it doesn't.

[Slide.]

When we consider expanding the score of PDUFA there's two specific places that APHA recommends consideration. In collaboration, let's talk about expanding the post-marketing surveillance and the focus on safety, to consider

the reality that safety of prescription drugs, there are three issues that come about.

We have challenges with the safety of prescription drugs when those drugs have risks that we don't know about. And so post-market surveillance and all of that work that helps us identify those risks is essential.

We also have problems with medications when we have the risks identified, but we don't do a good job of managing those risks. And so we need to do a better job of a systems-based approach to that risk management.

But there's a third area where we have problems with medications that often gets overlooked in this discussion, and it is a safety problem. And that's where we have benefits of medications, benefits where a certain patient population should be taking these products but they aren't because we don't have good dissemination of the information that we've learned in this post-market surveillance. And that's a piece that I'm not sure I've heard mentioned enough today.

It's something that we need to consider. When we talk about "safety," it's not just risks, but it's making sure that people who could benefit from the medications, that those benefits also get into the literature and, more importantly, into health care practice.

When we talk specifically about risk management, there's a constant call from pharmacists in practice to see a more systems-based approach to the very formal risk management systems that address products like thalidomide, lotrinex, and other products where we have had a specific risk identified, and are instituting a very rigorous risk-management program.

And recommendations that would help health care practitioners deal with those are having a means test to determine when a rigorous risk-management system is necessary.

Part of the challenge here is you may have a new drug coming to market where a specific risk is identified, and so a formal risk-management system is instituted, but there's a drug that's

already on the market that has the same risks and is not subject to the risk management system. So we do a very good job with the new drug, not such a good job with the existing drug, and may end up having clinical problems resulting from that.

To use standard tools to address similar risks: if we know that the risk with a protect is fetal exposure, do we have similar tools to address the risk of fetal exposure with thalidomide as we do with isotretinoin. And the Agency has made great progress in this area with the new isotretinoin program. We hope we'll see, as it goes live soon, where we now have some consistency among those tools to try and address that risk. But we must continue to make that Agency-wide and incorporate it better into the health care system.

We also need to do a better job in post-marketing surveillance of those risk-management programs. And so when we put those programs into place, what is the effect of those programs, and of those interventions, and are we truly managing the risks that we know about.

And, finally, that those systems work best when we have voluntary participation of health care professionals, rather than designating certain

health care professionals who should work with certain products. If you limit the number of health care professionals who work with certain products, you likely limit the patient access to those products. So you may minimize the risk, because you have fewer people using them, but you're not necessarily minimizing the risk in the right way, if people who should have access to those medications don't.

To summarize: what we call for is just a better collaboration, which we have seen in previous PDUFA renewals but need to continue to see in this cycle; collaboration between the Agency, health care professionals, consumer and the industry to make sure that we get the right medications on the market, but then that we also have the tools and the information to make sure that those drugs are used correctly.

Thank you.

MS. HENDERSON: Thank you very much, Ms. Winckler.

Next, I'm pleased to introduce Dr. Allen Veda, who is the executive director of the Institute for Safe Medication Practices--the ISMP--in Huntingdon Valley, Pennsylvania. He

previously served as Vice President of Clinical Operations at Mercy Suburban Hospital in Norristown, Pennsylvania.

Prior to his appointment as Vice President in 1995, Dr. Vaida held the positions of Director of Pharmacy, and then Assistant Vice President and Director of Pharmacy at Suburban General Hospital in Norristown, Pennsylvania.

Dr. Vaida has served as a trustee for ISMP from its incorporation in 1994, through his employment as executive director in the year 2000.

He received a bachelor of science in biology from the University of Scranton; a bachelor of science in pharmacy from the Philadelphia College of Pharmacy and Science; and a doctor of pharmacy degree from the University of Minnesota.

Dr. Vaida?

DR. VAIDA: Thank you. It is a pleasure to be here. What I'm going to do is just start, real briefly, for those of you that may not be familiar with our organization.

[Slide.]

The Institute for Safe Medication Practices is an organization whose mission is to educate about system causes of errors; translate

these errors into education; and to work closely although, as I mentioned before, independently with accrediting, regulatory, licensing, professional, manufacturers and government agencies, such as the FDA.

[Slide.]

The crux of where we get our information is through the Medication Errors Reporting Program, which is operated by the United States Pharmacopeia in conjunction with ISMP. As you notice, USP and ISMP are FDA MedWatch partners, and that is the information we get in through this program we share with the FDA. And, in turn, through the Freedom of

Information Act, we actually look at the medication errors that come through the FDA MedWatch program.

Now, you have my handout, and you're going to see an awful lot of pictures. And I'm going to go through some of these rapidly. And I'm not showing these to get down on manufacturers so much, or the FDA. But I just want to give you a view, through the eyes of ISMP where we still see some issues with names, labeling, packaging. And then just to sum up where we feel PDUFA funds should be reinstated, but that we do need some more emphasis on guidance documents for the manufacturers by the FDA.

[Slide.]

There are still issues out there right now with name problems. We get in a lot of errors through our reporting program. And as you can see here there's Depo-Subq Provera 104 Depo. This is given sub-cu, this is given IM. You can see the names, the numbers in these.

The insulin products: Novologs.

Here is a brand new product we've already

received five or six errors in, on this product: Omacor that has been mistaken for Amicar--especially verbally and written. This is something that's fairly new on the market.

[Slide.]

Now, there have been some changes, actually voluntarily, by some pharmaceutical companies. We did have mixups between products Serazone and Seroquel. It was actually packaging changes.

Lamictal and Lamisil. It was packaging changes in this.

[Slide.]

Zyprexa and Zyrtec: we still get a lot of mixups with that, although the company did do some packaging changes with this, and labeling changes.

And as I go through just with a couple of these, what I'm trying to build toward is: we do know a lot of these issues that are out there and should be changed. The FDA does have a list of close to 30 medications that they recommend tall-man lettering.

[Slide.]

As you can see here: "hydrALAzine" compared to "hydrOXYzine."

This holds true, too, with some companies have come too, Cis platinol. There's also Carbo platinol, to try to differentiate these two oncology drugs that are serious mixups.

So we've heard a lot all day about safety, but basically what I'm talking about here is preventable adverse drug events: those cause by errors. The drug may be what we consider safe and efficacious, but if it's used wrong, if it's packaged inappropriately there could be problems with the drugs.

[Slide.]

Here's a medication that's ben on the market, Cerebyx. If you notice here, the 50 mg per mL is prominent. This was involved in several medication errors and, in fact, several deaths. The packaging was changed, 100 mg. Because this was missed. So it shows here now: 100 mg in 2 mL. This is years ago.

[Slide.]

Here was another product: oncology drug, 20 mg/mL, that had several errors because no one noticed it was a 5 mL bottle, and they thought it was only 20 mg. So it was changed. The company changed the labeling.

[Slide.]

But then we wonder why this product is on the market: 100 mg/mL. This is after the labeling was changed on the other one. If you notice, it's a 2.5 mL vial. Ascorbic acid, 500 mg/mL, 50 mL vial.

[Slide.]

Depo-Medrol, 80 mg, 80 mg. This is a 1 mL, this is a 5 mL. What have we really learned from those other issues?

[Slide.]

And here, finally: 0.5, it's really 100 mL. These are package, marketing, why we need guidance documents with some of this funding.

[Slide.]

The USP Advisory Panel recommendations for

neuromuscular blockers, going back to '97. There are products that have "Warning: paralyzing agent" on this, but it's not across the board. And this is something that has been mixed up and is a fatal error.

[Slide.]

Same NDCs for active drug and diluent issues out there.

[Slide.]

We talk about dangerous abbreviations; not using trailing zeros. Here's packaging that has both: mics, that we've told them not to use the mu, and basically a 4.0--the trailing zero. In fact, there's a document now on the Library of Medicine that is actually on there for labeling etacrynic acid that actually has a trailing zero, and it doesn't have spacing between the strength and the units. That's actually up there.

Talking about never using abbreviations of drug names.

[Slide.]

This is a combination product: HCT. It

stands for hydrochlorothiazide. Years ago we reported on mixups between HCT being mistaken as "hydrocortisone," and hydrochlorothiazide.

[Slide.]

Same thing here, what we see with advertising. We always recommend with the "QD" it always gets mixed up with QID.

[Slide.]

And here's a product here--and, again, this is another recent product that's out. You're wondering, here's a product that's actually "mg/mL" is on the label, but it's dosed in micrograms, and it's administered in insulin units. This is actually for the patient--this piece here. You wonder: health professionals have a problem figuring this out; this is actually for the patient.

[Slide.]

Cafcit--here's basically caffeine citrate injection. We've reported on this several times with the mixup with the oral solutions.

[Slide.]

Packaging the same--and actually looking at Diprivan--propofol, which is basically an anesthetic, has been mixed up with fat solutions.

It was actually almost mixed up with rodoglide. This is actually something to help insert catheters in the cath lab, these products.

[Slide.]

Extended release suffixes, something the FDA was just involved in with the National Coordinating Council on Medication Error Reporting Programs, that actually took a look at suffixes, and the issues and problems that this causes.

I just have one up here: Cardizem, the diltiazem extended release. There's Cardizem CD, Caria XT, XR, and here's one with no suffix. These all stand for the same thing. This is just one. There's numerous products out there that you're trying to figure out why none of these are standardized.

[Slide.]

Here's a product: Welbutrin SR. Sustained release? Here's generic: "extended release." This

is the generic for this product. Not to get mixed up with Welbutrin XL, which is extended release, and is once a day.

So these are the type of things out there that we get reports in, and reports do come through the MedWatch program, too. But on packaging, labeling, things that we know.

I know that the FDA isn't really an authority over over-the-counter, but this is something else that I really think they have to take a real good look at to say: what could we do about some of the over-the-counter packaging and branding. I don't know if anything in the PDUFA could be used for something like that.

[Slide.]

This is a recent change that we had promoted. These were Tylenol children's. You notice here it says, "Medication per dos 80 mg." But there actually was two tablets, so it was 160 mg. This has since been changed, this came out.

[Slide.]

Maalox Regular, Maalox Total Stomach

Relief. We got an error report in on this, actually from a pharmacist who recommended this to their grandfather. Told him to take Maalox. Grandfather called and had bloody stools.

If you notice--you can't read this up here--but this is our same great Maalox, how it's advertised. But if you turn it over, this product doesn't contain any Maalox. There isn't any Maalox. This is bismuth subsalicylate in this product. But this is what we're seeing more and more of with brand-name extensions in over-the-counter products.

[Slide.]

Bisacodyl--Dulcolax stool softener.

[Slide.]

Kaopectate, that we all know. Here's Kaopectate, 180 degrees: stool softener.

So these are the type of things that I think need to be addressed. And although we've had several series of this PDUFA funding, these things need guidance documents.

[Slide.]

Finally, with preventable adverse drug reactions, this is something else that we should take a look at. We heard about the post-marketing

surveillance which is so important.

This is something else: respiratory depression, use of fentanyl patches, PCA, patient-controlled analgesias; local reactions.

What we are seeing through our reporting program is we're starting to get some adverse drug reactions. And when we go in the hospitals, we see a lot of adverse drug reaction reports that actually really aren't adverse drug reactions. They're preventable adverse drug events. They're preventable ones. These are errors. These are basically not using the right doses of these fentanyl patches. It's picking the wrong patients. Using heating pads over the patch. This is using them inappropriately.

These aren't really what we would consider adverse drug reactions.

[Slide.]

There is a need for guidance documents:

proprietary name safety testing. Canada, just two weeks ago, came out with a guidance document for look-alike, sound-alike names.

Labeling requirements--concentration strengths, as I said; font size, use of colors.

Drug suffixes, to define and standardize.

[Slide.]

We also need to have the FDA look at the information that it already has on the look-alike, sound-alike; a lot of the packaging that I've already shown you. We already know that is out there and it should be changed. Some of these things should be changed.

Mandate risk management programs for known safety issues. There are some drugs, there are some dosage forms that we know may be an issue. It doesn't mean that you have to keep those drugs off the market, but there should be some risk management programs in place.

They should also look to conduct some research. We don't have all the answers on the fonts and the colors and the use of tall-man

lettering, and actually which ones should you use. We have come out with recommendations, and we've actually seen a decrease in some errors. But we don't have all the answers on that.

[Slide.]

Communicate and work with independent organizations on post-marketing surveillance with the use of practical data sets; proactive monitoring.

Being to look at the preventable adverse drug reactions, as I mentioned about. This is something else that I think we really have to take a close look at.

[Slide.]

And review some advertising by manufacturers to eliminate the dangerous abbreviations and other known safety concerns.

And to look at the brand-name extensions for OTCs, if there's any way that that could actually be addressed. Although right now it's basically under the FTC.

Thank you very much, Dr. Vaida.

And last on this panel is William Zellmer. Mr. Zellmer is deputy executive vice president of the American Society of Health System Pharmacists,

a professional association that represents pharmacists that perform the full array of pharmacy functions in hospitals and health systems, including practice managers, front-line practitioners, and specialized clinical pharmacists who serve both in-patients and ambulatory patients.

He received his pharmacy education at the University of Wisconsin, and earned a master's of public health degree from Johns Hopkins University.

His responsibilities at ASHP include strategic planning, professional policy development, government affairs, public relations, and international affairs.

Please join me in welcoming Mr. Bill Zellmer.

MR. ZELLMER: Let me start by saying, with the name "Zellmer" I've had a lot of years of experience in sort of getting used to being last on the program. So I feel very comfortable in this

spot this afternoon.

I think I'll start by telling you a little bit more about the perspective that I'm representing. The society I work for represents pharmacists who practice in hospitals and health systems. And their goal is to help prescribers, the institution and the patient make the best use of medicines.

And, given this mission, ASHP members are involved in the following types of activities: establishing drug use policies through the formulary system, by serving on pharmacy and therapeutics committees; providing drug information to physicians and nurses; managing drug product acquisition and drug product inventory; preparing drug products for administration to the patient, such as by being involved in an IV admixture service; and managing drug product distribution; providing front-line clinical pharmacy services, including reviewing medication orders before the first dose is administered; monitoring patients for response to therapy and adjusting therapy as

authorized by the prescriber; and, finally, providing specialized clinical pharmacy services in areas such as intensive care, pediatrics, oncology and emergency care.

In short, ASHP members play a major role in fostering the safe and effective use of medicines in hospitals and health systems. And that's the perspective that I'm reflecting in my comments today.

Fundamentally, it seems to us that the FDA, as a major public health agency should be appropriated ample funds by Congress to achieve the full scope of its mission. In this way, the American public as a whole, through general tax dollars, will be supporting the vital work of the FDA, which benefits the entire population. I think in this regard we're aligned with the consumer groups who spoke earlier this afternoon.

However, we recognize that public policy has moved in another direction through PDUFA, and this is unlikely to change in the foreseeable future. So, given that political reality, we

strongly encourage Congress to use the tool of users fees to expand FDA's focus on drug safety issues.

PDUFA III addressed drug safety to some extent, but we would like to see the next reauthorization go much farther in this regard.

Now our written comments from ASHP will expand on this point, but I'm going to limit my oral comments this afternoon to just one facet of what we have in mind here.

Specifically, I want to discuss ASHP's belief that user fees should be increased to support a research program that would have the following three goals; first of all, improved post-marketing safety regulation; secondly, answer important questions about the effect of marketing practices on medication use safety; and third, develop models of patient care that bring actual medication use into better alignment with medication safety information.

We were impressed by some of the ideas of Daniel Carpenter of Harvard University, who

published an article last month in Health Affairs regarding allocating user fees to supporting a research program through the FDA. We like his suggestion that an FDA advisory panel should be charged with identifying the most important drug safety topics that merit research supported by user fees.

As stated by Carpenter, there are several ways that such research funds could be allocated. These include randomized controlled trials of widely used medications for chronic conditions; epidemiologic studies of post-marketing safety--Judy Cahill commented on that a few moments ago; and improvements in the FDA surveillance infrastructure. The results of these studies would be of immense value to pharmacists such as ASHP members in their efforts to foster the best use of medicines.

This past June, ASHP members in our house of delegates approved a policy position calling for an expansion of comparative clinical studies on the effectiveness and safety of marketed medications.

There may be occasions when these studies should compare the effects of a particular medication with other medications or with medical devices, or with procedures to treat a particular disease. A research fund derived from user fees and administered by the FDA could be drawn upon to support these studies, perhaps as a supplement to similar studies that are being supported by the Agency for health care research and quality.

Some of the resources of the user fee research fund should be devoted to evaluation of the medication use safety implications of certain FDA policies and industry marketing practices. For example, consider the case of direct-to-consumer advertising of prescription medicines. Although such advertising has more than doubled over the past five years, there is very little objective information on the effect of such advertising on the appropriateness of medication use.

It would be consistent with FDA's public health mission for the Agency to commission research on this topic, and the funding could come

from user fees that are allocated to research.

Finally, let me advocate that a portion of these research funds also be devoted to studying innovations in health care practice that may improve the safety of medication use. One of the big problems in health care is that insufficient attention is given to the evidence about how to use a medication safely. Susan Winckler talked about this just a little while ago in connection with her comments about a systems-based risk-management program.

The health policy community has largely ignored the prospect that my profession--the profession of pharmacy--could play a larger role in addressing this problem.

Consider the situation where it's well-established that a certain laboratory test must be performed periodically to ensure that the patient is not experiencing an adverse effect from the medication. It is easy to contemplate a system, using today's information technology, in which the pharmacy is a final check on whether that

lab test has been performed. If the test has not been done, a computer assisted decision tree could guide the pharmacist through a number of options, ranging from a dialogue with the prescriber to a decision by the pharmacist to dispense only a few days' supply of medication until the necessary laboratory work has been completed and analyzed.

It will be consistent with FDA's public health mission to stimulate demonstration projects of this nature on practice innovations, and the funding could come from user fees that are allocated to research.

In conclusion, the reauthorization of PDUFA is an important opportunity for the United States to marshal resources to expand our knowledge about medication safety. Hospital and health system pharmacists urge Congress to expand the program in the direction I've discussed. Doing so will give pharmacists firmer ground on which to pursue their efforts to help patients, prescribers and health care institutions make the best use of medicines.

Thanks very much for having us here today.

MS. HENDERSON: Thank you very much, Dr.

Zellmer. And than you to our panel.

Open Public Comment Period

MS. HENDERSON: It is now time for the open public comment period. And because I don't know how many people want to comment, I'm going to ask those of you who wish to provide public comment to come up to the first couple of rows and sit in the reserved seats so we'll know that you wish to make public comment.

I'm going to ask the FDA panel to please return to the stage so that you can sit and listen to the public comment.

And I will simply call you in the order in which you are sitting in the rows. So be careful which seat you take, or you may have to go first.

We're going to ask the public commenters--other than someone who has asked to please use her laptop, who will sit at the table up here--to use either one of the mikes on either side of the room

so you can address the FDA panel, if that's okay; and to please introduce yourselves so the FDA panel, as well as the panel knows who you are.

So, with that having been said, why don't I start with you, since you wish to come up.

MS. ALLINA: Thank you for the opportunity to speak today. My name is Amy Allina. Unlike the previous speakers, I'm not used to going at the end of the day. But I'm happy to have the chance to speak anyway.

I am the program director at the National Women's Health Network, which is a member-supported advocacy organization that works to improve the health of all women through influencing policy and supporting informed individual decision-making in health care. And we do a lot of work with the FDA, including having worked on the last round of PDUFA reauthorization, working with many of the patient and consumer advocacy organizations who have already spoken today.

At the time of the last reauthorization we raised several concerns about the effects that the

PDUFA had had on the Agency and on the public health. We were especially concerned that in order to fund the quicker review that PDUFA was designed to bring about, the Agency had been required to drain resources from other essential activities like post-market research and surveillance, and inspections, and regulation of medical devices. And we were also concerned that the shorter review times put a strain on the review staff that was causing problems as staff were leaving and the Agency was losing experience and expertise.

Now, raising those concerns did not mean that we were opposed to faster approval of products. We represent consumers, we represent patients, and we also feel those concerns. But we were worried that speed was coming at the expense of safety. And we were worried that the Agency's review staff didn't have the opportunity to raise questions about safety; that when they did, such questions were being disregarded because the Agency was more concerned with meeting PDUFA deadlines; and that following approval, the parts of the

Agency responsible for ensuring post-market safety had been starved by the PDUFA financing structure in such a way that meant that they weren't able to fill the gap and clean up the problems that were being created by flawed reviews. So, taken together, we saw this as something that would really undermine the FDA's ability to ensure safe drugs and devices, and to play its critical role in protecting the public health.

So we raised those concerns. They were heard to some degree, but I think probably not given the weight that they would be given today. In September 2002 the GAO issued a report, that's already been mentioned today, that confirmed many of the concerns that we articulated.

I'm not going to go through all the findings of the report, but it did include findings that funds for activities other than review of drugs and biologics had become a smaller part of FDA's budget since the enactment of PDUFA; that the number of FTEs for drug and biologic review had increased, while FTEs for other activities had

declined. And I think we saw that trend continuing today.

The GAO report also found that these shifts had serious consequences. At the time the report was published, the data showed that in FY '02, inspection of medical devices had decreased, and there were 1,000 fewer FTEs allocated to programs like food safety and monitoring of devices after they were on the market. And the report also confirmed some of the concerns that we had raised about how implementation of the PDUFA program was leading to both an increased workload and very high turnover rate in the review staff at FDA; a turnover rate that was higher than that at other Federal public health agencies.

So, as the FDA presenters and some others have noted, PDUFA III gave the Agency some flexibility to spend limited PDUFA funds on some safety activities, but I think it's also pretty well established at this point that there have been developments since the time of PDUFA III that have demonstrated that the safety concerns that were

raised at the time of that last reauthorization are still an issue. The patient safety problems with Vioxx and SSRIs are just the highest profile examples.

And there have been Congressional hearings to look this, and there is a much more widespread understanding today of the serious problems facing FDA. The New York Times, just last December, after reporting on some of those problems, actually editorialized specifically on PDUFA, and said that the program has "grievously distorted the Agency's drug safety program;" that the Agency has had to cannibalize programs to monitor the safety of drugs after they're on the market to keep up its review of new drugs before they're allowed on the market.

So today, as the FDA prepares for the next reauthorization of PDUFA, the context is fundamentally different than it's been in any of the previous rounds. Public concern and policy makers' understanding of the need to strengthen the FDA's ability to address drug safety problems is very strong. This creates a real opportunity for

change that I hope we'll see the Agency embrace.

I do believe that the user fee program as it exists detracts from the FDA's ability to address safety problems, both because of how it directs the Agency resources, and because of the client-funder role that it establishes for the industry that FDA is supposed to be regulating--that FDA is regulating. I don't mean to say that you're not.

Given that, given the way the program affects that relationship, it's essential for the public health that we establish an FDA structure that protects the independence of the Agency's decision-making. So structural changes are needed to protect FDA's independence and its integrity, and to enhance drug safety and enhance the public health.

The establishment of the PDUFA performance and management goals has focused evaluations of the programs on process. We're talking about time to approval, number of meetings, and things like that, rather than on what should be our real goals:

increasing the number of people helped by FDA-approved products, and decreasing the number of people who are harmed by them.

Toward that end, the National Women's Health Network encourages both the FDA and the Congress to incorporate some of the excellent suggestions we have heard today from our colleagues on the consumer advocates panel, and a number of suggestions we heard from other panels, including patient advocates, and the health care professionals who spoke just before me.

We want to express our support for research to evaluate comparative effectiveness data on products approved for the same indication, and making that information available to consumers so that we'll have the information that we need to choose the products that best meet our needs; legislative reforms to dealing PDUFA revenues from industry-designated priorities; drug safety initiatives like those included in the Grassley-Dodd legislation; enhanced authority to enable the FDA to take decisive and timely action

when safety concerns are identified; explicit authority to limit general marketing, and specifically DTCA of new drugs that have been approved based on studies of carefully limited study populations, where there are outstanding safety questions about use in the broader, more diverse general population; proactive monitoring of post-market safety, using safety data bases from both the public and private sectors.

And then, finally, I want to echo the plea that's been made by a number of other speakers that both patients and consumer advocates should be included in PDUFA negotiations, and not be relegated to a pro forma consultative stakeholder role.

Thank you.

MS. HENDERSON: Thank you very much.

The gentleman in the front row.

MR. ROSEN: Good afternoon. My name is Bill Rosen, and I'm here to read a statement on behalf of CDISC, the Clinical Data Interchange Standards Consortium.

Patient health is related to the ability of the pharmaceutical industry to produce safe, effective products. Likewise, delivery of new

medicines to waiting patients is related to the expeditious submission and review of data generated during product development by the FDA. Standardization of the format and content of the clinical data submitted within an application will ultimately lead to improved efficiencies in the submission and review process. This, in turn, will enhance pharmacovigilance by providing a clearer safety picture for new products.

Therefore, CDISC proposes to use a portion of PDUFA fees for the purpose of implementation and training on the use of CDISC data standard currently included in the Electronic Common Technical Document Draft Guidance. The Clinical Data Interchange Standards Consortium is a not-for-profit pharma industry group whose mission is to develop and support global platform-independent data standards that enable information system interoperability to improve

medical research and related areas of health care.

CDISC has published a comprehensive data standard known as "The Submission Data Tabulation Model"--SDTM--for the submission of all clinical data from pharmaceutical and biotech companies to the FDA. Once received by FDA, the data is to be loaded into the Janus data warehouse for use by medical reviewers and, at a future time, statisticians during the application review process.

Process change, computer infrastructure, software tools and training are necessary to realize the efficiencies that the CDISC standard offers to a new review process, and is consistent with the original intent of PDUFA, which states: "Fees authorized by amendments made in this subtitle will be dedicated towards expediting the drug development process and the process for the review of human drug applications."

Given that the application review process will change as a result of implementation of the CDISC standard, it is imperative that this change

be managed properly and implemented efficiently.

We recommended the following areas receive dedicated funding from PDUFA to ensure successful implementation so efficiencies can be realized: dedicate a program director and implementation team during the phased roll-out of the new process, computer infrastructure, new tools, data standard and training across all review divisions; develop and implement a change of management process improvement plan with metrics; develop and implement an Agency-wide communication plan to provide ongoing information and feedback on program progress; develop specific training plans for the data standard tools, best practices, as well as whatever information needs to be discussed with sponsors to ensure a successful submission and application review; create and maintain a help desk to answer all questions regarding the new process, during and after implementation, for both agency and industry.

We also recommend the following performance goals. All applications to the agency

will use the CDISC standard by the year 2010. Basic tools, infrastructure and training to support submissions using the standard will be in place consistently across all divisions by second quarter 2008, or two years after this funded project starts. Eliminate the need to submit patient listings, profiles and annotated CRFs by third quarter 2008, or 2.5 years after the funded project starts.

Application review time will be reduced by a minimum of 10 percent when using CDISC standards to submit data within an application 2.5 years after this funded project starts. Application review time will be reduced by a minimum of 20 percent when using CDISC standards within an application five years after the funded project starts.

Dedication of a portion of the PDUFA fees for this vital project is a natural use of PDUFA monies, and will allow for the successful adoption of a new, improved, more effective and efficient review process.

Signed: Dr. Rebecca Kush, founder and president of CDISC; and Dr. Steven Ruberg, chairman of the board of CDISC.

Thank you.

MS. HENDERSON: Thank you very much.

The gentleman in the front row. Wherever you're most comfortable.

MR. KIRSCHENBAUM: My name is Alan Kirschenbaum. I'm with the law firm of Heimenfeltz and McNamarra in Washington, D.C.. And I'm here to present a statement on behalf of the Council on Radionuclides and Radiopharmaceuticals, more conveniently known as CORAR.

CORAR is an association of 17 companies that manufacture and distribute radiopharmaceuticals and radionuclides, primarily for use in medicine and life-science research.

Unlike many of the other speakers here, today I am not going to talk about problems and issues that have arisen in the user fee program to date. Instead, I'd like to talk about a problem that will arise down the road in two or three years

if steps are not taken to avoid it.

CORAR submitted a citizen petition on August 31st of this year requesting that FDA establish a class waiver under which manufacturers of positron-emission-tomography drugs--or so-called PET drugs--would be exempt from multiple establishment fees, and would have to pay, at most, a single establishment fee for each NDA.

For those in the room who don't know what PET drugs are, these are not animal drugs as the acronym would suggest. They're human radioactive drugs that are produced by tagging a substrate compound with a positron-emitting isotope. After they're injected, the isotope is distributed to certain tissues in the body, and using a PET camera, nuclear physicians produce computerized images of biochemical processes and tissue structures based on measurements of the different rates at which the isotope emits positrons.

Physicians then use these images to diagnose, stage and monitor diseases such as focal epilepsy, certain cardiac diseases, dementias, and

certain cancers.

One of the distinguishing features of PET drugs is their extremely short half-life. They have a radioactive half-life that's measured in minutes or hours. So they have to be used very soon after they're produced. For this reason, PET drugs are prepared by facilities only as needed, and they have to be in close proximity to the medical facilities where they're used.

Because of the short half-life of these drugs, a commercial manufacturer that supplies PET drugs nationally, or even regionally, has to have multiple manufacturing establishments located throughout the U.S. or throughout the region. And NDA that's sponsored by a commercial PET manufacturer might specify 10, 20 or even more manufacturing establishments. At this years establishment-fee rate of $264,000, you can see that a sponsor with 10 facilities would have to pay $2.7 million approximately; one with 20 facilities would have to pay over $5 million, and so forth.

And this is in contrast to conventional

drugs, both diagnostic and therapeutic drugs, where one or a small number of establishments is sufficient to supply the whole country.

The reason this has not been a problem to date is because of another unique feature of PET drugs, which is their unusual regulatory status. There is now, as a result of the Food and Drug Administration Modernization Act of 1997, there is a moratorium on the regulation of PET products as new drugs. And this moratorium lasts until FDA establishes procedures by which PET drugs are approved under the new drug approval process, and also establishes good manufacturing practices for PET drugs. FDA just recently proposed a rule for CGMPs for PET drugs, and the moratorium will last until two years after that rule is finalized.

During the interim, manufacturers of PET drugs can voluntarily submit NDAs, but after the moratorium is over, they will be required to submit NDAs, and therefore required to also pay user fees. And that's when the establishment fee problem will become acute.

We think that establishment fees should be reduced or waived for commercial manufacturers of PET drugs. When Congress enacted the FDAMA

provisions that established the moratorium, it asked FDA to establish special procedures for marketing applications and CGMPs and, in doing so, to take into account the--quote--"special characteristics of PET drugs and the special techniques and processes required to produce these drugs."

We think that these special characteristics and processes also ought to be taken into account in the user fee program in the next PDUFA period also. We think that, as a class, PET drugs qualify for either the barrier-to-innovation waiver or public health waiver provisions.

They are innovative. PET imaging is an extremely sensitive technique that produces images of biochemical processes, not just the structure of tissues and organs, so that it can detect diseases before significant changes in body structure are

evident. And, of course, earlier and more specific detection increases the changes of effective treatment.

Clinical PET is rapidly growing for use in cancers, heart disease, neurological disorders. I think just last week Dr. Gottlieb, I think in a speech, at least as reported by the trade press, made reference to a new collaboration between the FDA and the NCI to use PET scans as a development endpoint in cancer trials.

And we think that large annual fee, multiple annual establishment fee assessments could create a disincentive to the development and the supply of PET imaging agents. We also believe that it's in the interest of public health not to discourage commercial PET manufacturers from making PET drugs readily available at numerous facilities throughout the U.S.

Without a lot of PET centers in close proximity to medical centers, patients would have to travel, in some cases, hundreds of miles to the nearest medical facility that offers PET drugs.

So, we think it would prudent and fair to determine that human drug applications for PET drugs would, under a class waiver, be subject just

to a single establishment fee. And I would add that there's precedent, dating just from this year, for class waivers for certain classes of drugs. In April, there was a guidance document providing for a class waiver for certain fees for HIV drugs proposed for use in the President's Emergency Plan for AIDS Relief. And also this year the FDA decided to extend this barrier-to-innovation waiver to certain combination products so that they didn't have to pay duplicate application fees for an NDA in a PMA. So there is precedent for this.

And I'd just conclude by saying: here's one area where we have ample chance to avoid a problem before it arises, and we urge the FDA to provide a class waiver so that PET drug companies who supply these products nationally, or over a large region, are not subject to multiple establishment fees annually.

Thank you very much. I appreciate the

opportunity to present that statement.

MS. HENDERSON: Thank you, Mr. Kirschenbaum.

Oh, I was going to say "the gentleman in the red tie," but that would be any one of you down there, wouldn't it?

The gentleman in the paisley tie.

MR. ELLIS: Good afternoon. My name is Milton Ellis, and my company is Rare Disease Therapeutics, located in Nashville, Tennessee.

My company was founded in 1991, and the goal was to create a company that focused on the development of orphan drugs, and take advantage of the incentives that the Orphan Drug Act provided. To my knowledge, we're the only biopharmaceutical company in the United States that is exclusively devoted to the development, registration and distribution of orphan products.

We do it because we know that large pharmaceutical companies can't do it. It's not practical for them to do it, and otherwise this patient population would go untreated.

My goal today is to provide you a picture of what it is like to develop orphan drugs, either by ourselves or through licensing.

We have all the same obligations as large pharmaceutical companies, with just a bare fraction of the resources. As a matter of fact, today 25 percent of my company is here, and that would be me.

We also have to pay user fees, which have become a barrier to innovation in meeting the needs of these rare disease patients. So far we have one marketed orphan drug, and four other orphan drugs that are in development. All of these drugs are for conditions that affect fewer than 500 people in the United States. One of these products is an anti-venom for scorpion envenomation, solely for the State of Arizona. And that's because of the Sonoran Desert and the species located there. It will probably produce less than a million dollars in revenue for that condition, and we'll have to pay over $350,000 in user fees.

And had we known that we would not get a

waiver for this very small ultra-orphan product, we would probably not have ever started the development of it for the United States market.

We have one marketed product right now called Offiden [ph] and it treats hereditary tyrosinemia Type I. It's a condition that affects fewer than 500 children worldwide, and less than 100 in the United States. This condition is a genetic disorder, and it manifests itself as the infant fails to thrive within weeks or months after birth. If untreated, the disorder is fatal in the first year of life, and the only other option is an orthotic liver transplant.

Currently, we have 78 patients in the United States that are being treated with Offiden. This means that every patient is being assessed what I'd like to call a "pass-through tax" more than $5,000 a year, just to offset the user fees. The large-selling, large-volume drugs, patients are paying pennies per year to cover the same user fees that we have to cover.

You hear Diane Dorman speak earlier, and

gave the comparison of the DayPro patient that would be paying 33 cents as a pass-through per year, where we're paying $5,000.

Offiden was originally developed as a herbicide at AstraZeneca, and it was found to have utility in treating this disease. And they put it on the shelf. That's another example of big pharmaceutical companies' not wanting to take responsibility for developing these small products.

It was licensed then to Swedish Orphan International, and we licensed it from Swedish Orphan International for United States, Canada and South America.

We were not able to acquire the NDA rights owned by Swedish Orphan, and this is understandable, because a lot of companies want licensees to handle their products, but they don't want to lose the ownership of their intellectual property. So that meant we were responsible for maintaining the product in the United States. This is quite common with the license for the U.S. market.

There also came the responsibility for meeting all the regulatory requirements in the United States. This includes having to pay user

fees on our approved products in all of its dosage forms, and also pay user fees on the facility in which it's manufactured. This became problematic for us, because the 1992 FDA Draft Interim Guidance on User Fees considers waiver requests only from the NDA holder, not from the entity responsible for paying the user fee.

Further, that same interim guidance provides waivers only to small businesses, defined as those with less than $10 million in gross revenue. This is much too low, as well as wrongly focused on how big the business is. It's much more relevant to ask how much revenue is generated by the orphan product itself. I would add that neither of these FDA interpretations is required by the terms of the PDUFA statute; only by the definitions put in the draft interim guidance 13 years ago.

For three years we've had to pay user fees

on Offiden; fees that now amount to $389,000 a year. We are responsible for these fees, but not the NDA holder. We are small enough, but the NDA holder is not.

Further, when we have two and three orphan products on the market, we are likely to exceed $10 million in gross revenue. This same amount of money--$389,000--could fund an additional clinical trial on an orphan drug or a new indication. It could support more educational information for prevention and treatment; or become the seed money for another orphan drug that we might license.

Waiver of these user fees might also allow us to stabilize the price of our orphan drug even when our costs are rising.

Rare disease patients benefit under all of these scenarios. In fact, if Offiden user fees had been waived, these monies would have been used to pay part of the cost of new post-marketing requirements imposed by the FDA. Ironically, now that these children on Offiden face full and long lives rather than early deaths, we must go back and

do reproductive toxicology studies on the compound. The cost of these studies could exceed $1 million, and that's for 78 patients.

AS you can see, we are caught between the public policy goals of the Orphan Drug Act, designed to make it a little easier to develop products for small populations, and the Prescription Drug User Fee Act, which has the worthy goal of funding a bigger and stronger FDA.

Simply put, when these two laws collide, we get smashed.

Earlier today Ms. Dorman outlined the NORD position on how to fix PDUFA. NORD wants to help small company with truly worthy goals who want to develop orphan drugs for rare diseases. We support the NORD position, and feel that any orphan drug with revenues less than $25 million should be exempt from waiver fees.

Thank you very much.

MS. HENDERSON: Thank you very much, Mr. Ellis.

Last, the gentleman standing with his

laptop.

MR. HENCH: Hello. My name is Milt Hench. I'm the technical services director for Regent Medical, a company down in Norcross, Georgia. We're a mid-size medical company that sells a well-known antiseptic, and we've come here today to talk about the PDUFA.

While user fees under the PDUFA for prescription drugs might seem reasonable, for some non-prescription OTCs, such as we have, that fall under PDUFA, the fees are excessive. In addition, recent large increases in PDUFA user fees have made an already bad situation much worse for us.

Last year we submitted a PS change for the way our product is applied to the hands, which required a user fee in excess of more than a quarter of a million dollars. The user fee for the review of the submission that filled one one-and-a-half inch notebook.

In addition, we paid almost $200,000 for the studies that were submitted. So we paid close to a half a million dollars to simply change the

way an antiseptic is applied to the hands; the majority of which was PDUFA fee.

This year, the PDUFA fee has been increased, from more than a quarter of a million dollars to more than a third of a million dollars.

The Prescription Drug User Fee Act was intended for prescription drugs. And user fees were initiated to speed up the review times. And we understand and appreciate that. In addition, they were based upon the complexity of prescription drug applications. However, some non-prescription OTC drugs fall under PDUFA and are subjected to the same fees as prescription drugs, with simpler submissions, simpler applications, simpler products.

While it's government's job to regulate, it's also government's job to provide an economic climate that stimulates business. These jobs must be kept in balance. And at this time, things seem to be out of balance for us.

User fees are hurting our company's ability to innovate, compete and grow our product.

Money that could be spent for research and development is going for user fees.

We believe that the current situation needs to be changed to separate the fees and regulations that are applied to prescription drugs which often sell for hundreds of millions to billions of dollars, at very high margins, and are called "big pharma," as we heard today.

From some OTC products, non-prescription such as ours, which often sell in the millions of dollars, at much lower margins, and should be called "small pharma"--and I'd like to call them "orphan drugs," like the previous speaker--they currently fall under the PDUFA Act.

To help separate prescription drug user fees from OTC product user fees, we would like to see the FDA solicit comments about OTC user fees via the Federal Register. In addition, a gradient user-fee structure for clinical data should be included in the Federal Register solicitation for comments.

User fees should be based upon the scope

of the clinical study and its complexity, proportional to the size, complexity and nature of the clinical study, not just because it's a submission.

We therefore petition for a solicitation of comments by the Federal Register regarding separating user fees for some OTC products from prescription drugs; making user fees proportional to the scope of the clinical study to be reviewed--the larger the study and the more complex the submission, the larger the user fee.

Thank you.

MS. HENDERSON: Thank you, Mr. Hench.

Do we have any additional comments from the audience?

[No response.]

If not, then I'd like to thank our FDA panel, thank our audience very much for your participation and your patience.

Good night.

[Whereupon, at 4:11 p.m. the meeting was adjourned.]