U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

+ + + + +

FOOD AND DRUG ADMINISTRATION

+ + + + +

PRESCRIPTION DRUG USER FEE ACT (PDUFA)

+ + + + +

PUBLIC MEETING

+ + + + +

MONDAY, APRIL 12, 2010

The meeting came to order at 9:00 a.m. in the Plaza Ballroom of the Rockville Hilton, 1750 Rockville Pike, Rockville, Maryland. Terry Toigo, Facilitator, presiding.

PRESENT:

TERRY TOIGO, RPh, MBA, Director, Office of Special Health Issues, FDA
JOSHUA SHARFSTEIN, MD, Principal Deputy Commissioner, FDA
ROBERT YETTER, PhD, Associate Director of Review Management, CBER, FDA
JOHN JENKINS, MD, Director, Office of New Drugs, CDER, FDA
THERESA MULLIN, PhD, Associate Director of Planning and Informatics, CDER, FDA

ALSO PRESENT:

PANEL 1 - FDA PERSPECTIVES:
JANET WOODCOCK, MD, Director, CDER, FDA
KAREN MIDTHUN, MD, Acting Director, CBER, FDA

PANEL 2 - CONSUMER PERSPECTIVES:
WILLIAM VAUGHAN, Consumers Union
KIM WITCZAK, Woody Matters
SALLY GREENBERG, National Consumers League
DIANA ZUCKERMAN, PhD, National Research Center for Women and Families

PANEL 3 - PATIENT PERSPECTIVES:
DIANE DORMAN, National Organization for Rare Disorders
MARC BOUTIN, JD, National Health Council
DANIEL PERRY, Alliance for Aging Research
ELLEN SIGAL, PhD, Friends of Cancer Research

PANEL 4 - HEALTH CARE PROFESSIONAL PERSPECTIVES:
MARCIE BOUGH, PhD, PharmD, American Pharmacists Association
KASEY THOMPSON, PharmD, American Society of Health-System Pharmacists
BARRY DICKINSON, PhD, American Medical Association
MARK DEL MONTE, JD, American Academy of Pediatrics

PANEL 5 - SCIENTIFIC AND ACADEMIC EXPERT PERSPECTIVES:
CHRISTOPHER MILNE, DVM, MPH, JD, Tufts Center for the Study of Drug Development
JOSH BENNER, PharmD, ScD, Brookings Institution
BECKY KUSH, Clinical Data Interchange Standards Consortium (CDISC)

PANEL 6 - REGULATED INDUSTRY PERSPECTIVES:
DAVID WHEADON, MD, Pharmaceutical Research and Manufacturers of America
ANDREW EMMETT, Biotechnology Industry Organization
BRIDGET ELIS, JD, Plasma Protein Therapeutics Association

T-A-B-L-E O-F C-O-N-T-E-N-T-S

Welcome
Terry Toigo, RPh, MBA
Director, Office of Special Health Issues, FDA 5

Opening Remarks
Joshua Sharfstein, MD
Principal Deputy Commissioner, FDA. . 10

Panel 1 - FDA Perspectives
Janet Woodcock, MD
Director, Center for Drug Evaluation and Research FDA. 16
Karen Midthun, MD
Acting Director, Center for Biologics Evaluation and Research, FDA. 35

Panel 2 - Consumer Perspectives
William Vaughan
Senior Health Policy Analyst, Consumers Union 42
Kim Witczak
Woody Matters 51
Sally Greenberg
Executive Director, National Consumers League. 66
Diana Zuckerman, PhD
President, National Research Center for Women and Families. 80

Panel 3 - Patient Perspectives
Diane Dorman, National Organization for Rare Disorders. 93
Marc Boutin, JD, National Health Council 100
Daniel Perry, Alliance for Aging Research. 113
Ellen Sigal, Ph.D. Friends of Cancer Research. 124

Panel 4 - Health Care Professional Perspectives:
Marcie Bough, Ph.D. PharmD, American Pharmacists Association 139
Kasey Thompson, PharmD, American Society of Health-System Pharmacists. 154
Barry Dickinson, Ph.D.
Director, Science and Biotechnology, American Medical Association. 165
Mark Del Monte, JD
Director, Department of Federal Affairs, American Academy of Pediatrics. . . .180

Panel 5 - Scientific and Academic Expert Perspectives
Christopher Milne, DVM, MPH, JD
Associate Director, Tufts Center for the Study of Drug Development 193
Josh Benner, PharmD. ScD
Research Director, Engelberg Center for Health Care Reform, Brookings Institution 217
Becky Kush, Ph.D.
President and CEO, Clinical Data Interchange Standards Consortium (CDISC) 238

Panel 6 - Regulated Industry Perspectives
David Wheadon, MD
Senior Vice President, Scientific and Regulatory Affairs, Pharmaceutical Research and Manufacturers of America. 252
Andrew Emmett
Director, Scientific and Regulatory Affairs, Biotechnology Industry Organization. 266
Bridget Elis, JD
Assistant Director, Regulatory Policy, Plasma Protein Therapeutics Association 283

P-R-O-C-E-E-D-I-N-G-S

(9:04 a.m.)

FACILITATOR TOIGO: Okay. Good morning, everyone and welcome to this public meeting on the Prescription Drug User Fee Act, or PDUFA as we have come to call it. I am Terry Toigo. I am the Director of the Office of Special Health Issues at FDA and I'm going to be your moderator for today.

As you all know PDUFA authorizes the FDA to collect fees from manufacturers to help offset the cost of reviewing new applications to market drugs and biologics. Over the past 17 years there have been four consecutive PDUFA programs. The current legislative authority for PDUFA IV reauthorized in 2007 by the FDA Amendments Act will expire in September 2012.

Today's meeting is scheduled well before that 2010 deadline to gather input from stakeholders who will be affected by this legislation before the agency begins

discussions with the regulated industry on PDUFA's reauthorization.

So that is the purpose of today's meeting. Now I'm going to explain a little bit about the format that we are going to use in order for us to listen to your comments and hear your concerns.

As you can see from the agenda we have a full day. We'll start with remarks by FDA's Principal Deputy Commissioner, Dr. Josh Sharfstein. Josh will be followed by perspectives from Dr. Janet Woodcock, the Director for the Center for Drug Evaluation and Research, and Dr. Karen Midthun, the Acting Director for the Center for Biologics Evaluation and Research. And then Karen and Janet are going to be followed by five panels with representatives from diverse stakeholder groups; consumer advocates, patient advocates, health professionals, scientific and academic professionals, and then the regulated industry.

Each presenter was asked to provide his or her perspectives on the PDUFA program. FDA provided two questions in the Federal Register, announcing this meeting and that the intent was to focus the comments from our stakeholders.

These two questions: What is your assessment of the overall performance of the PDUFA IV program thus far. The second question: What aspects of PDUFA should be retained, changed, or discontinued to further strengthen and improve the program.

Speakers were asked to focus on process enhancements and funding issues, not policy issues. FDA policy issues are beyond the scope of these reauthorization discussions.

We'll have 21 presenters and we have allowed ample time at the end of the day to hear additional comments from those in the room. Each individual presenter will have no more than 15 minutes for their presentation

and as time allows my FDA colleagues or me may ask clarifying questions.

My job for today is to keep us on time so, speakers, as you get close to your allocated 15 minutes I'll kindly remind you that your time will soon be up. I'm apologizing up front for any intrusions but our speakers knew about the plan in advance and so we want to be fair to everyone.

As I mentioned, we do have time allocated at the end of the day for other speakers who will have registered in advance. The final session, that open session, will include an FDA listening panel.

If you have not registered and you plan to speak in the open session, please see the folks at the registration desk and sign up to speak and we are going to certainly try to accommodate all people who want to speak.

So then finally before we get started just a few housekeeping details. We'll have two 15-minute breaks; one in the

morning at 10:45 and one at 2:45. Lunch will be from 12:00 to 1:00. You're on your own at the hotel or there are plenty of places within short walking distance that you can get to lunch. The restrooms are outside the ballroom across the hall by the Regency Room.

Parking is complimentary. If you parked, at the end of the day they will lift the gate. If you're leaving early you have to see the folks at the registration desk and they will direct you how to get your parking complimentary.

Then one final detail. Your feedback is really important to us, both positive and negative. It helps us plan for future meetings so don't hesitate to share your comments with FDA employees at the registration desk, or you can always e-mail me and that's Theresa.toigo@fda.hhs.gov.

I'll stop there and turn the microphone over to Dr. Sharfstein for some opening remarks.

DR. SHARFSTEIN: Thanks, Terry.

Good morning, everybody. I'll try that one more time, PDUFA meeting. Good morning, everybody. I'm very excited to be here. I know that for most of the world the start of the PDUFA reauthorization process is not a seminal event but for those in this room and elsewhere who are very focused on FDA this is kind of like opening day or maybe the first World Cup qualifier that culminates in the World Cup a few years down the road. I will never get to open up, I think, for opening day of a World Cup qualifier so I'm real excited to have been asked to be here to open this process.

I'm Josh Sharfstein, Principal Deputy Commissioner at FDA. I think this is going to be a very important process that will start today to renew strength in the PDUFA program in 2012.

As you all know, PDUFA fees combined with appropriated dollars support a

wide range of activities that are critical for the effective and timely review of drug applications. This includes both pre and post-market activities and regulatory oversight both of effectiveness and safety.

FDA is the only regulatory authority in the world that requires companies to submit the raw data collected in clinical trials to assure that we can replicate the analyses and results reported by the sponsor and to do our own independent analyses of the data.

Doing this review requires a multi-disciplinary team. These teams include doctors, pharmacologists, toxicologists, experts in drug chemistry, biostatistics, biopharmaceutics, clinical microbiology, risk communication, risk management, and sometimes others.

In addition, our clinical site investigators inspect clinical trial sites for data integrity and our manufacturing site

inspectors inspect drug facilities for drug quality. Our surveillance teams increasingly utilizing large sets of health care data to ask and answer safety questions and FDA is building a new active surveillance system called Sentinel.

Short-changing these activities would mean missing important evidence of both benefit and risk and would affect the work of the agency and the health of the American people.

At FDA we are committed to continuous improvement. I hope all of you visit the new FDA website www.fda.gov/FDATRACK and see the agency's new program performance system which when fully implemented will track more than 300 measures and keep projects of 100 FDA offices.

I'm curious how many people here have seen the FDA-TRACK website. If you have, raise your hand. Good. I hope you are engaged in that and send us your ideas on FDA-

TRACK and watch the numbers that get posted.

The PDUFA process also benefits from continuous improvement. Over the years the program has been enhanced with each reauthorization and this is due in no small part to the input of public stakeholders.

Today marks the beginning of the next stage in this process. With the new authorities of the FDAAA in effect for a little over two years and the start of this process for the next reauthorization a little over two years from now we are seeking your input. We are interested in all comments on how to make this program work better for public health.

Public health perspective on PDUFA recognizes both the benefit and the risk of medication therapy. In every community, including my own, our friends and neighbors are suffering and dying from diseases with no good treatments. Are there changes to PDUFA processes that can facilitate the development

and review of truly innovative products and better health for these patients.

Across the country many patients also suffer from serious adverse affects of medication therapy. Some of these only become known after widespread marketing because clinical trials with limited numbers of patients will not have the power to detect rare adverse events. Are there changes to PDUFA processes that can help identify serious risk earlier?

Other medication risks are well known and avoidable and yet they are not always avoided. FDA has launched the safety initiative to work with the medical profession and others to address these avoidable risks. Are there changes to PDUFA processes that can better support safety use?

Improvements and regulatory signs can help sponsors and the agency make judgments about both the effectiveness and safety better and sooner. Are there changes

to PDUFA processes to encourage the right kind of regulatory science research and the use of new approaches to modernize the drug review process.

These are just some of the questions to be explored. We want to hear your thoughts on these issues as well as other topics. We also want your candid assessment of what is working and what is not working with PDUFA. If my experience at the agency for the last year is any guide, I think we'll get your candid assessment today.

We look forward not only to hearing you today at this meeting but also to leave the submissions for a public docket open for 30 days beginning today. As outlined by Congress FDA will then begin negotiations with industry as well as have regular meetings with patient and consumer groups to continue discussion of their views.

After negotiations are concluded FDA will publish the minutes of negotiation

meetings on our website. We will also publish the administration's proposed recommendations for reauthorization on our website and establish a docket to obtain public input on those recommendations.

In addition, we will hold a public meeting on the proposed recommendations. FDA will consider the public views and comments and revise recommendations as necessary based on that input. The administration's final proposed recommendations will be submitted to the House and Senate authorizing committees in January of 2012.

Thank you for being here at the beginning and for your continued participation along the way. Good luck today.

FACILITATOR TOIGO: Thank you, Josh. I'll ask our two center directors to come up for the first panel. Dr. Woodcock and Dr. Midthun are going to start us off with the FDA perspective.

DR. WOODCOCK: Thanks very much,

Terry. Good morning to all of you. I'm delighted to be here and to be able to help kick off this start on the next PDUFA round. I'm going to present the Center for Drug's perspective on PDUFA.

You heard from Dr. Sharfstein and the agency-wide perspectives and then Karen will be talking about the same perspectives from the Center for Biologics' point of view. I would emphasize that we are pretty much in sync here. We simply regulate somewhat different products and, therefore, have slightly different perspectives on what PDUFA is doing.

To go back in history at the time when the user fee program was first started up, why was that? It's easy to forget what times were like then and what problems were being addressed. What was happening with FDA was a slow, and unpredictable from the point of view of industry, drug review process.

We had what was called the drug lag

where products were approved earlier in Europe than in other regions that had regulatory systems much faster than the United States. We had a meeting approval time of two years in this country for standard application.

That means, of course, half of them took longer than that. Some of them took considerably longer than that. This was because it took maybe a year or two for somebody to pick up the application because we were so understaffed. These were submitted and then they sat there until somebody was freed up from their work to pick up that application and do it.

I would remind you that we also didn't have many of the complex programs that we have today in 1992. We didn't have any pediatric work that we now do evaluating the drugs for their use in children recommending different trials that need to be done, evaluating the results of those trials and so forth.

We also did not have a sophisticated drug safety system in the United States. Of course, we are still building that. I would say we still don't have a sophisticated drug safety system but we are well on the way to building one.

So that was the situation. User fees added resources for more review staff and this was to eliminate the backlog and then to meet goals for timeliness for new applications. This funding has continued and it ensures that appropriate resources are brought to this task of drug review.

Nowadays compared to them we have a streamlined more predictable process but also process that does many more activities than was done in 1992. We have continued to reduce the review time, the time where a cycle of review to occur and, as a result, this has shortened time to actually drugs getting on the market.

Although the PDUFA program, I would

remind you, has nothing to do with us whether or not we approve a drug. It simply has to do with the timeliness of the review process that we now have enough staff that we can initiate the review when an application is submitted versus waiting until a team is freed up. We manage to goal so we have instituted project management and other activities to make sure that review process is well managed.

How does this program work? Well, most of you know the fee funds are added to base appropriated dollars and then FDA has agreed and each one of these four programs over the years to commitments to certain performance -- these are goals that we commit to that are decided by negotiation.

The last PDUFA program there was input by the industry and there was also input by many other stakeholders. The performance commitments are focused on improving the process.

Something that people don't focus

on that you really need to recognize about this program is that user fees pay for services that directly benefit the fee payers beyond the benefits that are derived by the general public from, say, taxpayers' dollars. This distinguishes a user fee program which is basically a fee for service versus funding from tax revenue. This is a fundamental difference in these types of two funding streams.

The performance goals that we have. We have a large number of performance goals under the user fee program. What most people focus on is the first line in this chart which is the review of NDAs and BLAs and efficacy supplements and the timeliness of that.

I will reiterate this doesn't mean we approve them within this time. This means that they go through a review cycle. We do a complete evaluation of what is submitted within this time.

Six months for something that is a

priority that appears to be an advance over existing therapeutic options and 10 months for standard application. These have a complicated formula whereby they can be amended if additional information is submitted by the applicant during this time period.

This process of additional submission and also the process whereby the end of the review process we may find that the application does not meet our standards and, therefore, we ask for more information.

This leads to something called resubmissions whereby the company, the applicant, then sends in additional information to the application. These also have goals for review of the resubmission depending on how complicated the resubmission is, how much information is contained within it.

In addition, once a product gets on the market the sponsor may wish or the manufacturer may wish to change something

about the manufacturing process. FDA regulates these carefully. We often require approval by the FDA before the process is changed and, therefore, their goals for us reviewing these.

This obviously is important both for the public as well as for the manufacturers because it's really important. Often these impact on the quality of the product and, therefore, it's very important that we have timely and up-to-date review and allow changes in the way the products are manufactured.

In addition, somewhere during the program, perhaps two cycles ago, we had something called the special protocol assessment. This has goals associated with it.

What this is is that the regulatory agency and the sponsor reach agreement on specific questions around registration trial on the protocol for how to do that

registration trial or trials and there is a formal process whereby questions are submitted and the agency will meet with the sponsor and then opine on these questions.

This is very important because -- both for the public because patients should not be submitted to trials that are not going to meet their objectives so volunteers should not be going into trials unless those trials are designed in a way that will meet the objectives that they are being conducted for.

They are also very important for the sponsors. These trials may cost hundreds of millions of dollars to conduct and, therefore, you need to get it right from the start. I think from a societal point of view these SPAs are very important. However, they are very time consuming for the FDA because we are basically committing to certain design features in advance of the trial being done.

Another goal has to do with clinical holds. This is when a development

program, an investigational development program is halted by the agency. It's called a clinical hold. Often it's because of safety issues and there are negotiations and time goals around how we resolve those and how we get back to the sponsor and so forth.

Then there is a very large category of PDUFA performance goals around the industry or the applicants, whoever is developing products, having meetings with the agency. We have to have goals on scheduling the meetings. We have to have goals on the minutes and all sorts of things. This creates a huge number of goals that the agency is tracking and trying to perform against.

So those are some of the performance goals for PDUFA. All of them either have to do with timeliness and efficiency of the review process or giving appropriate advice to sponsors during the development programs.

And during the last four PDUFA

programs, the scope of PDUFA as far as what is covered and what the goals are has expanded over time. As I said, in PDUFA I, it was really mainly about the drug lag and about speeding up the review process for applications and those performance goals were introduced.

In PDUFA II we saw primarily a lot of these new goals such as the meeting request, dispute resolution, the special protocol assessments and other goals I spoke about. In PDUFA III we realized that in PDUFA II we had really underbid the contractor so to speak and we hadn't received enough resources. There was a very enthusiastic and unanticipated response by applicants to having all these meetings and having much more interaction with the agency.

Now, some people may be concerned about this but I do remind you that all of these development programs involve human volunteers and so it is in the best interest

of not just the industry but of the public that the regulatory agency be very engaged in what the development programs are, how these trials are done and so forth.

Anyway, it cost more because of the huge industry response to getting input from the agency. We were expending much more effort than anticipated on meetings, giving regulatory advice and so forth in these SPAs.

Therefore, we put a workload adjuster into user fee calculations and we also agreed to try to get the management of the user fee program up to a -- or the new drug review process really, up to a higher level of management oversight which are good review management principals and practices.

For the first time in PDUFA III there was a small contribution for three years after post-market to direct safety oversight of marketed drugs. This was kind of a landmark.

The PDUFA IV program that we're in

the middle of right now had further increases in base fee funding and we readjusted the workload adjuster to more realistically reflect the amount of work that was being done by the agency.

Similarly, there was increased funding for drug safety and this is ramping up over the four years of the program. As I said, we still don't really have the resources that are needed to have a world class post-market drug safety program. However, this is certainly helping us.

In addition, of course, we are now having a lot of issues with the globalization of manufacturing and drug safety on the manufacturing side. The agency has multiple challenges in drug safety not only related to the inherent risks of drug products but also to the risks introduced, if you will, by the manufacturing globalization.

Anyway, we've ramped up funding in PDUFA IV. We also agree to issue new

guidances on trial design. Some of those are out in draft. We also have new process requirements for the grounds and all sorts of things under the FDA Amendments Act that was passed several years ago.

Again, additional workload issues imposed upon the program in addition to the additional funding. We kind of see this neck and neck over the years so we get more funding for the program under PDUFA but then we have pediatrics with the Amendments Act, with the Modernization Act. We have new requirements imposed that kind of suck up some of this funding.

So there are two sides of PDUFA that people react to in the public: that patients have greater access now to new drugs and biologics because there are two factors here. One is just the speed of the process but that is probably lesser than the fact that having a predictable review process with predictable standards can incentivize

innovators to develop products in that area.

For example, vaccines are doing better now because there is a feeling that there is a predictable path for that new vaccine to get on the market. Same with other therapies. If there's a feeling that there is no pathway available for development, or it's very murky or unclear, then developers move away from that and the pipeline diminishes in that area.

Here are the numbers. There have been quite a few approvals under PDUFA III and then we're in the middle, as I said, of PDUFA IV. I would point out the efficacy supplements. These are very important and they have really gone up under the user fee program.

These are important because this is the evidence base that people are talking about now for health care quality. We need to know whether drugs work or not or other medical interventions. In the past we put

drugs out on the market and then they would simply be used off-label for all these other indications without an evidence base. These efficacy supplements actually represent cases where the sponsor has gone have studied the drug in the new indication and they have submitted a supplement so that information can get on the label. That's very important and that's what is being done in pediatrics as well.

That is the positive side. The other side is that people are concerned that the PDUFA goal structure where FDA is partially -- where review activities are funded by user fees and they stimulate increased interactions between the agency and the manufacturers. This makes FDA too responsive to industry. These are kind of the two sides of the coin.

Now, the point is, though, whatever the source of the resources in the United States the FDA needs significant resources to

do our work in a timely manner. Right now about 65 percent or more of human drug review funding comes from user fees. This is by no means the entire funding for the FDA programs in drugs and biologics but the part that has to do with the process of review of new human drugs is majority funding from user fees.

I would point out that we are the only regulatory body in the world that looks at patient-level data. Dr. Sharfstein alluded to this. We are kind of like the quality control group for the world in this but it is labor intensive to do a review this way as opposed to reviewing summary data that is submitted by the manufacturers.

This labor intensive quality of the review that FDA does at the patient data level and at the detailed manufacturing level and at the individual animal data level and so forth this requires more resources. It's possible FDA could do this another way, simply look at summary data, but that would mean, I think,

that nobody would be looking at the detailed patient and animal and so forth level data.

This work right now supported by user fee resources that really allows us to have this function that we perform and we have no preference on the source of the funding but the bottom line is it's a resource-intensive activity that we perform, this audit at this level. If it weren't to come from user fees, either we wouldn't be able to do it or we would need a different source of funding. Those are sort of the bottom line implications.

I'm almost done. The timeline for this process, this new process now, is we're beginning to reevaluate how we should run the PDUFA program. We are having a public meeting and we'll have a docket to follow. We will be evaluating all the comments submitted to the docket and we will hold discussions in the summer and in the fall with industry under public stakeholders. We are going to have an

iterative process.

By January of 2011 we hope to complete our industry and stakeholder discussions. As Dr. Sharfstein said the administration would take a review of that and then the administration would develop recommendations and those recommendations then will be sent to Congress. Congress doesn't enact user fee goals. It enacts the program and kind of endorses whatever the goals might be.

Although in recent years in the legislation Congress as added additional things to various PDUFA programs that have been passed. Public participation obviously is a very important part of this process. PDUFA has been successful but not everyone is comfortable with how it's structured.

If people are concerned, we want to hear not only what are your concerns but what are you proposing as an alternative. That's really the issue is your alternative, for

example, that we not review the data at the individual patient or animal level, manufacturing data at the level of detail that we review it.

We want to hear from you about how the program might be modified along with what are the opportunities posed and the risks of these modifications. We have to take these both into account. This is our every-five-year opportunity to obtain input from all the stakeholders.

I thank you very much. Sorry I went over.

FACILITATOR TOIGO: Thank you, Janet.

DR. MIDHUN: Good morning. I'm Karen Midthun, Acting Director of CBER. I think that Janet really provided a great platform so actually I think we'll make up time in my presentation because she really laid out the fundamentals so I think I will just make some points to reinforce a number of

the issues that she underscored.

I think what is really important to recognize is that prior to the Prescription Drug User Fee Act of 1992 there was no statutory or obligatory timeline for the review of biologics license applications or for NDAs for that matter. What PDUFA really did was bring about a structure that allowed timelines and predictable causes as Dr. Woodcock was indicating.

It really provided the impetus, the focus, and the resources that allowed CBER to develop a focused review process that supported efficient and effective scientific reviews of biological products. As Dr. Woodcock noted, as FDA we look at the primary data for manufacturing, for clinical trials, for toxicological studies, for biopharmaceutical evaluation and this really is a very labor-intensive process.

PDUFA really started to provide the resources needed to do that. Also it led to a

structure and a process with regard to the review management practices that really permeate what we do at the center in terms of really having efficient process where you can track things, where you can really understand what your business process is and so it's really brought about a very solid science-based review process.

I think that also it's important to recognize that we have products of ever-increasing complexity and, again, the resources to deal with these products has been provided and been critical to this process. Our numbers are much smaller relative to CDER's. As you can see in PDUFA III we had 16 standard BLAs, 10 priorities, with regard to efficacy supplements, 22 standards and one priority.

As Dr. Woodcock noted, these efficacy supplements are really critical as they really are an underpinning for additional indications for which the product has been

evaluated and add to a very important science and clinical database.

Obviously PDUFA IV approvals are much smaller as we are only partway through the PDUFA IV cycle. Also as Dr. Woodcock noted, with the most recent PDUFA it provided us with additional resources for safety surveillance which has also been very important for activities.

Also, as Janet mentioned, the authorizing legislation that has come through with a different PDUFA has often brought new requirements. For example, the most recent FDA Amendments Authorization Act really brought about many new requirements for pediatrics, for safety, and for a number of other things which we had to intercalate into the process of reviewing our products.

Obviously as you fit more activities into a given time space this can be a challenge and I think we have been dealing with some of those challenges as well.

I think this is really an opportunity where we want to hear from you, our stakeholders, about PDUFA, about the benefits, the concerns and, as Dr. Woodcock mentioned, where there are concerns or where there are any ideas you want to bring to the table to talk about the alternatives that you would want us to take into account. We really look forward to the start of a public discussion.

As Dr. Woodcock outlined, there is going to be a lot of opportunity downstream to really consider the input and have further discussions. We really welcome that. Thank you very much and we really look forward to today's discussion. Thank you.

FACILITATOR TOIGO: Thank you, Karen and Janet. I know you were nervous as to why I wasn't cutting Dr. Woodcock off for 15 minutes but they had 30 minutes and they worked it out and we are still on time. I'm true to my word.

The next panel is our Consumer Panel. If all of our consumer presenters could come and join me in the front I would appreciate that. Is Sally here?

While the Consumer Panel is coming to the front of the room, I'm sure one of the questions on people's minds is what is going to happen to the information and the viewpoints that FDA receives today. I can assure you that in addition to the transcription of today's meeting, there are FDA staff from the PDUFA steering committee and others who are taking notes here today.

The presentations and the comments from the open public session as well as written submissions to the docket will be carefully considered as we look at the features FDA should be proposing for the PDUFA V program.

The docket announced in the Federal Register notice for this meeting is open until May 12th so we have plenty of opportunity for

comments. I see that the Panel had the same struggles as I did because you expect that the steps are going to be here. There are steps over there. It's easy to climb but I see we have all done the same thing.

Bios for our presenters were available when you registered so I'm not going to read bios in the interest of time. The purpose is to hear from people. You can read about them and most of them when they begin their comments will be telling you who they are speaking for.

We have four members from the consumer community, Diana Zuckerman, Sally Greenberg, Kim Witczak, and Bill Vaughan. Each of them are going to present perspectives from their experience and their organization. Do you have the order you want to go in? Bill, you are going to start? Okay. I knew we heard it had juggled but I didn't get a chance to talk to you. If you want to go first, then Bill is going to start.

MR. VAUGHAN: Thank you for this opportunity for Consumer's Union which is the independent nonprofit publisher of Consumer Reports mostly known for our automobile issues but we also try to help people get good buys on safe pharmaceuticals.

We are also members of the Patient Consumer and Public Health Coalition, some of whom are speaking today. I have a long written statement. I think some copies might still be left at the sign-in desk. In the webinar, Dr. Jenkins' data on PDUFA IV progress I thought was very impressive so congratulations to the FDA.

We think PDUFA V is a further opportunity to make historic dramatic life-saving advances in the rapid safe development and use of prescription drugs. We appreciate Congress' decision in the PDUFA IV to include consumers more clearly in the renegotiation process. You'll be negotiating with the industry and having discussions with us and

that has the faint odor, you could even say strong odor, of when I was little sitting at the kid's table during Thanksgiving. You always sort of want to be at the main table and I hope in the spirit of the law and to make this a good process that it will be an open process and that at a reasonable rate the minutes of the meetings with industry will be made public and shared with us so that we can have discussions and negotiations that are meaningful.

I would say to the extent that minutes are taken of, I think the law says, "discussions with representatives of patient and consumer advocacy groups," and if consumer's union is involved, we would be happy to see it all open to the public and press and we urge the industry to make the same kind of commitment.

I'm going to list a number of issues we believe need more resources. Whether appropriations or user fees we can all

debate but definitely more resources are needed. The federal government's long-term budget crisis makes it clear that we can't rely just on appropriations in the future.

On advertising, Kim Witczak is going to be talking about it some, and we agree with her and we believe the entire DTC effort needs to be reformed, strengthened, and expanded with more resources in this area, especially to monitor this new wild west of internet advertising.

Just a suggestion. If the FDA would require extensive corrective ads when it finds an abuse as it did the Yaz ads the extra cost and embarrassment might make the enactment of pre-DTC review user fee system more welcome or more acceptable in 2012.

Also in PDUFA V we hope a system might be developed which would enable or require certain new drugs to actively involve patients say through internet or voicemail pinging in safety reporting. We believe drug

package labeling is still confusing, inconsistent, and inadequate. We support immediate implementation of the type of drug fact box called for in the health reform laws, under Jack Reed's amendment, which has long been advocated by Drs. Schwartz and Woloshin. A simple quantitative facts box showing relative efficiency and safety would help sweep away the years of confusion in this area but still require additional resources to implement.

To improve safety and save consumers money we urge that the FDA take a really, really major role in comparative effectiveness research. The drug facts box I just mentioned would contribute to CE but the FDA can take two other CER actions that will hugely benefit safety, effectiveness, and consumer savings.

First, we urge aggressive implementation of the Sentinel Program. Additional resources should contribute to

ensure that this powerful new research tool is fully and always used and not left idle. Second, it is past time to transition to a new system in which drugs and devices are tested against the currently approved best practice.

By testing against best practice, and wherever possible placebo, all of the St. John's Wart, for example, whenever possible placebo, the FDA can help promote comparative effectiveness research arm consumers with the best information and improve clinical practice.

The off-label use has got to be addressed. Sure, OL is legal and maybe often beneficial but we worry that it's on the rise. It's not always wise. Maybe it's getting riskier. Drug companies all too often skirt the rules.

Consumers are totally in the dark about what it means. An inappropriate OL adds to wasteful spending. The government appears to be in a kind of losing game of whack-a-mole

with the industry repeatedly assessing billions of dollars in fines for OL promotion which the companies appear to treat as a cost of business.

What a waste. Those fines can make these user fees look kind of like chump change. We are going to spend about two years haggling and quibbling over the size of the user fees and Pfizer just paid fines about four times the amount we're collecting in user fees this year. There has got to be a better way. Think of how that money could have been used on research to finally answer these questions does this stuff work or doesn't it? The current system is ridiculous.

We are interested now and certainly in PDUFA V a major effort can be made to deal with OL. Why not each year have the FDA identify 10 or so of the most commonly prescribed OLs and through FDAAA authorized studies, randomized trials, Sentinel databases determine what works and what doesn't.

On clinical trials a major part of FDAAA was reforming the registration and reporting of clinical trials which is still being implemented. The last two-and-a-half years have brought us many new reports continuing to show that the system of trial registration, reporting and publication is terribly flawed.

The flaws are so pervasive, serious, and unethical that we fear for the success and integrity of the new clinical trial program. It would be naive in the extreme to think that for-profits will every voluntarily fully disclose trial data that hurts them. Caveat emptor is not good enough when it comes to life and death for highly technical trial data.

Therefore, we urge now and through increases in PDUFA V a stronger system of sampling and auditing in an annual percentage of trials. On the issue of protecting patients in trials you currently check about

one percent of clinical trial sites and these sites are increasingly overseas.

If a person could buy futures in scandals, I would invest in international clinical trials. This is further disaster waiting to happen and you need to increase the level of inspections, we think dramatically.

I appreciated Dr. Woodcock's discussion of trying to help or protect patients in trials and making sure that they are not needlessly subject to trouble. We would like to see more in that area, or at least understand more.

Several years ago Dr. Nissen, Cleveland Clinic's Dr. Nissen, testified, I am aware of a class of drugs where more than a dozen compounds showed serious toxicity resulting in termination of development but without a single publication or results.

I'm not sure how that happened 12 times. We would like to work with the FDA more on that. Actually, we want to urge

Congress, getting a little bit into policy here, urge Congress to require the eventual public reporting of Phase 1 trials either as part of the approval process or, in the case of a withdrawn or failed effort, after a suitable period of time.

This information would advance science, save lives and resources and speed new drug development and meet a moral obligation, as Dr. Woodcock said. People who subject themselves to an experiment should have the results of that risk contribute to the world of knowledge.

Finally, our written statement talks about the need for more research in ensuring generic safety and public understanding of generics, where and when to use them and how safe they are. As well as doing reduced drug errors due to confusion in names, labeling and packaging.

We thank the FDA for their daily hard work on behalf of the public and for your

time today. Thank you.

FACILITATOR TOIGO: Thank you, Bill. That is a long list and if you are all working together and each one is going to add that many, it's going to be a really long list.

I think, Kim, are you going to go next then? You don't have slides, right?

MS. WITCZAK: No, I don't. Good morning. My name is Kim Witczak and I'm from Minneapolis, Minnesota. Thank you for inviting me today to participate on the Consumer Panel at the start of the reauthorization process.

It seems like just yesterday we were working with Congress to make improvements to PDUFA IV and appreciate the opportunity to be part of the conversations to ensure that the consumer voice is considered and addressed in the draft documents going forward.

I'm here today to represent the

voice of thousands of families who live every day with the consequences of the current drug safety system. Unfortunately I know only too well what it's like to lose someone because of unsafe drugs.

On August 6, 2003, my life changed forever. My husband of almost 10 years was found dead hanging from the rafters of our garage of Zoloft-induced suicide at age 37. Woody was not depressed, nor did he have a history of depression or any other mental illness.

Woody had just started his dream job at Vice President of Sales with a start-up company a few months prior and was having difficulty sleeping so he went to his doctor, his general practitioner, and Woody was given a Zoloft sample pack.

Five weeks later Woody took his own life. No cautionary warning was given to him or me about the need to be closely monitored when first going on these drugs or dosage

changes. Never once did we question the drug. Why would we? It was FDA approved, heavily promoted as safe and effective and it was handed out by his doctor.

This is the reality for Americans. We trust our doctors who assume that the FDA and drug companies did their job to ensure that the drugs that we're taking are safe and effective.

Just this weekend I went to the doctor for a sore throat that I've had for a couple of weeks and I have to say with all the work I do I still just kind of trusted my doctor to give me the drug that I was going to take.

From the beginning something didn't add up about Woody's death so we started researching the only thing that had changed and that was Zoloft. Our journey for the truth led us to the FDA, HHS, Congress, and the courts. We were active in getting black box warnings added to antidepressants to

children under 18 in 2004 and eventually extended to young adults in 2006.

From confidential drug company and FDA documents as well as other information learned through a lawsuit we quickly learned that antidepressants weren't the only class of drugs with problems. There was an overall issue with the drug safety system in our country so we set out to make a difference with what we could to make sure that what happened to our family didn't happen to another.

As I mentioned earlier, we worked with Congress alongside other consumer groups to help strengthen PDUFA IV to include stronger drug safety and FDA reform legislation. I was also invited to testify before the Senate Health Committee on these issues.

I'm happy to see that the public voice is being heard at the beginning of this process. To ensure it being successful it

must be an open process throughout the negotiations and it sounds like today that is the intention. It is my hope that it is and that it's not just a good PR move.

Wouldn't it be nice to go to Congress in 2012 with a draft agreement that is reached between the FDA, the industry, and consumer groups so we are not waiting unnecessary time out there and lobbying dollars fighting for basic things that should be included.

So one way to guarantee it is to make sure we have a seat at the table or at least that the minutes are made available on a timely basis. This goes a long way to ensure transparency and openness.

Over the course of today and the next several months we will hear many recommendations and a wish list of things that should be included in PDUFA V. Where are a few that I would like for you to consider.

There has to be a culture of

openness and transparency. The FDA is a scientific organization and the heart of any such organization is open-mindedness, willingness to look at new data, and flexibility. The scientists and agency personnel must be able to disagree and not feel pressure by management or the industry to change or withhold findings or data. Public health is at risk.

As seen with the antidepressants as early as in 1990 with Dr. David Graham stating that Eli Lily didn't adequately address the suicide issue with Prozac and later with Dr. Andrew Mosholder pressure to withhold suicide data during the pediatric trials in 2004.

I really thought that after this last round of PDUFA IV drug safety legislation and with the new administration and management that this would change. I don't know anymore than what I've been reading in the news about the CAT scans and the dissent amongst some of the FDA scientists that are questioning the

unnecessary CAT scans.

However, if it seems that the internal culture has not changed and we need to make sure that the agency allows and supports healthy debate and peer review.

Number two, the FDA needs some authority to require and mandate drug companies to do additional studies on off-label uses. The FDA knows that both of our drugs are being prescribed off-label. My husband was given Zoloft off-label for insomnia.

Many of the anti-depressants and anti-psychotics are currently are being prescribed off-label and everyone knows it. The FDA must have the authority to mandate further studies. Right now we should be studying the drug cocktails that are being given to our returning vets.

In the past couple of years there have been few drugs companies caught promoting drugs off-label, as Phil mentioned earlier,

with Pfizer and Neurontin. These are enormous finds and often are just considered cost of doing business and can be buried in shell companies or absorbed by insurance policies.

Instead of punishing with huge fines why not make them prove it once and for all. I know clinical studies are expensive but so are the fines. Ultimately it's the consumer who is paying the price by taking drugs that have little or no benefit or even deadly side effects. If the drug works off-label, then drug companies should get it approved and marketed for the new use.

The third one is health consumers and doctors choose the best treatment. Instead of seeing if a new drug is better than a sugar pill, or basically better than nothing, require that it is also tested against current best practices treatments already on the market.

All the FDA information on comparative effectiveness and drugs should be

made public to health doctors and patients, make the best evidence-based treatment choices.

Like in the case of anti-depressants where placebos had out-performed the drugs in most cases of mild depression, yet are being over-promoted and over-prescribed putting people at risk often without their knowledge.

Give the public all the information and options. Also think about the potential savings in the healthcare system if we know that the new more expensive drug isn't any better than what is available on the market or a non-drug treatment.

Next we need to make sure that we are getting honest reporting at clinical trials. The last round of PDUFA in the reform was in registration reporting of clinical trials. It's too early to know if it's actually working but we know that we do need to see major improvements in the quality of

clinical trials.

There is a long history of scientific dishonesty in conduct and reporting that seems to become accepted as cultural norm. We need more than just summaries. A Phase 1 trial result should be included, too.

I'm not naive to think that drug companies are going to voluntarily report so that means the FDA has to be more aggressive in reviewing as well as being open when information comes from the outside, especially when information is learned from legal action.

One thing that was particularly hard for me to discover was the side effect that killed my husband was known very early in the clinical trials late in the 1980s and was withheld. Plus with more and more of the trials going on in the country we need to have the resources to make sure that we are monitoring them.

The last one I'm pretty passionate about is sappy advertising hype. I've spent

my entire 22-year career in advertising and believe DTC is responsible for the increased demand of prescription drugs resulting in putting people at unnecessary risk.

There is a direct link between the media ad spending dollars and the drugs that are having issues such as Vioxx and antidepressants being the perfect example. Personally I would love to see no drug advertising allowed. However, I'm realistic and know we are fighting an uphill battle not only with pharma but media lobbyists, etc.

With that being said, I do believe we could have separate mandatory DTC user fees. Obviously the voluntary program didn't work. Why would anybody want to pay for it when basically you just get a slap on the wrist and it's worth taking. There is no real punishment. You may have to pay a small fee or do a corrective ad but by that time the damage has already done and the money has been made.

The FDA needs to reform and strengthen the DTC effort. Ads for new drugs shouldn't be allowed for a specified period of time while side effects are still being discovered. As we know, the greater chance of side effects emerge when masses start taking the drugs.

Drug companies are marketers and are going to adverse the drugs with the largest potential target market resulting in higher sales. This is why patients need to be involved in safety reporting. One of the ideas that I brought up during Senate Health during the last round of PDUFA was the idea of adding the FDA MedWatch information to the advertising. I am happy to report that it is required on all print advertising. However, I'm disappointed that it was not included on television commercials and that it needed to be studied further. It seems like a stall tactic as it could be several years away before this information is added to TV

commercials.

MedWatch should be included on every form of communication which reaches consumers, especially TV commercials with a large number of viewers. I know the other side will say that it serves as a public service announcement encouraging consumers to go and talk to their doctor about a particular disorder.

If that's the case, they could really do a public service by being proactive and letting consumers know that they can report side effects to the MedWatch program. There is an opportunity to revamp the MedWatch program to add a more consumer friendly site with something like drugsafety.gov.

I have several ideas around this so it would make it more consumer friendly and would love to share them. As part of PDUFA V part of the funds could go towards this as well. It seems like it's something that the drug industry could support as well.

I applaud the FDA for recently holding a two-day hearing on social media. We have entered into new territory and the FDA has to think outside the box regarding to social media. Obviously I'm not saying anything new but the FDA needs more resources to manage this new landscape. It changes too fast and it can't be done on the traditional DTC pass.

Lastly is conflict of interest on advisory committees. It needs to be resolved. I know you're in the process of going out and finding consumer reps right now but that is just something that I'll be watching.

On a separate note, but still related, I'm currently a patient representative on the Psychopharmacologic Drugs Advisory Committee and have learned that patient reps are not always included at these meetings like consumer rep counterparts. It is often determined by the advisory committee chairperson whether he or she feels that a

patient representative is necessary.

Like consumer reps, patient reps should be mandatory in every FDA advisory committee. There needs to be more input from a consumer patient point of view represented at the table.

To conclude I would just like to say thank you for inviting me and listening and being open minded and willing to continue to work with all parties. It would be great to bring forward the best most time-intensive 360 degree agreement to Congress.

I would ask that you remember Woody for his story represents thousands of Americans who have personally paid the price. Your decisions have real-life consequences and you guys have the ability to make some changes so thank you.

FACILITATOR TOIGO: Thank you, Kim. Thank you for sharing your husband's story. Two things. MedWatch is part of my office, so separate from PDUFA, I would like to talk to

you about how we could be more consumer friendly.

Dr. Sharfstein this morning mentioned FDA-TRACK and I think if you go look there is an area on patient representatives we'll be tracking and our goal is to include patient representatives at all advisory committee meetings and we'll be monitoring our own performance so you can check FDA-TRACK.

Sally, if you would come to the podium and present next.

MS. GREENBERG: Thank you, Terry. Thank you, Kim, for coming and telling your story. It's really important to hear patient perspectives.

Good morning. I'm Sally Greenberg. I'm Executive Director of the National Consumer's League and I want to join the chorus of consumer reps thanking the FDA for meeting and for allowing us to provide our perspective and perspectives and viewpoints on PDUFA.

Let me tell you just a few things about the National Consumer's League. We are the nation's oldest nonprofit consumer education and advocacy organization. We were founded in 1899. We provide government business and other organizations with the consumer's perspective on numerous policy issues including child labor which goes back to our roots, privacy, food safety, medication safety and medication information.

From the first Pure Food and Drugs Act passed in 1906 to the more recent FDA Modernization Act, NCL has been working often alongside the FDA to ensure that the public is adequately represented and protected. It's in this context that NCL is calling on the FDA to seize the upcoming PDUFA reauthorization as an opportunity to critically examine the impact of the program and make meaningful changes to enhance the safety of drugs in this country.

I would like to turn to the specific question posed for this public

meeting. That is, what is our assessment of the overall performance of the PDUFA program thus far?

NCL believes that the work of FDA is of such critical importance that it really warrants funding from the general treasury and funding that is commensurate with many of FDA's responsibilities. However, given budgetary constraints we understand that the user fee system is the only viable option at the moment to ensure adequate funding.

There is an ongoing perception that the FDA has become among consumers, and I think probably patient representatives as well, has become too close to the companies over which it has regulatory authority. This is exacerbated by the fact that the public has relatively little opportunity for input into the rules governing the 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's leading health care consumers, the agency's most important constituency out of the loop.

Over time the system has improved somewhat with PDUFA IV including consumers in the renegotiation process. However, as Bill Vaughan from Consumer's Union as noted, in order for the consumer community to fully engage in this process we need to know what industry is proposing during the negotiations, not when they are completed.

For this reason we believe that minutes from the negotiations with industry should be made public so the consumers have a chance for bona fide input. Until consumer interest are directly represented in the final negotiation process, the FDA will truly not be serving its most important constituency.

NCL fully supports the ideal that enhanced drug approval processes benefit everyone. However, faster approval does not

necessarily mean better. Getting safe and effective drugs to the market as quickly as possible is a laudable goal. Quicker approval has it drawbacks. Rapid approvals can mean, and have meant, that consumers are exposed to unnecessary and often deadly risks.

While we are pleased that PDUFA IV allocated over 29 million of the annual user fee revenue, which is about 7 percent, to go to patient safety initiatives. We would like to see that percentage increase. This would reinforce the principle that FDA believes patient safety requires an equal place alongside a speedy approval process.

Let me now turn to the question posed of what aspects of PDUFA should be retained, changed, or discontinued to further strengthen and improve the program. We commend the FDA for the drug safety activities that have been implemented under PDUFA IV. However, much more needs to be done.

NCL has a number of additional

suggestions but we are going to focus on DTCA review, reporting adverse events, and off-label use. We also support many of the suggestions already made by members of this consumer panel related to generic drugs and clinical trials.

First on DTC. NCL has long been interested in assuring that consumers receive accurate and useful information about their health care including about the safe and effective use of prescription drugs.

With over $4 billion spent on direct to consumer advertising in 2008 and over 91 percent of Americans reporting that they have seen or heard advertisements for prescription drugs DTCA has become an integral part of communicating information to patients. Consumers are continually exposed to these ads and it's FDA's responsibility to make sure they are accurate and not misleading before they reach the public.

As CU has noted, since the

voluntary DTC user program introduced under PDUFA IV failed NCL suggest the following actions. First, the FDA should be granted the authority to require that all DTCA ads undergo agency review before dissemination. Without the authority to make a review a condition of broadcasting product sponsors have no incentive to submit their ads for agency review.

Second, user fees should be assessed for the review of the full spectrum of media reaching consumers, not just television ads which is the current situation under PDUFA IV. Under PDUFA V print, radio, internet and television should be included.

To review only TV ads is highly problematic given the extent to which campaigns tend to be coordinated and integrated across multiple media in order to maximize impact. User fees should be a mandatory part of the submission of any DTCA ad regardless of the medium to the agency.

The revenue derived from the fees could be used to support a number of currently under-funded agency activities including the hiring of additional staff to review and respond to industry feedback in a timely fashion.

We support inclusion of a drug facts box in the DTC ads as has already been mentioned by the previous two speakers. Such a fact box would contain both understandable risk and benefit information. The box could contain published data including information on possible outcomes with and without the drugs.

Many ads use vague qualitative terms to describe the benefits of the drug. The absence of actual benefit data may lead consumers to believe that a drug is more effective than it actually is.

We also need more disease awareness messages and communications without the promotion of a specific drug. If we really

want to improve public health DTC user fees should be employed to improve education on disease awareness, health conditions, diet, exercise, and drug adherence.

Lastly, we support agency authority to place a moratorium on all DTC advertising for new drugs deemed to have inadequate safety information. Based on available safety data the agency could be given latitude on determining the appropriate one for the moratorium on a product-by-product basis.

NCL will also support a third provisional status for some drugs which would allow limited approval of a product to appropriate patients. This would mitigate the likelihood of inappropriate use and overexposure while additional post-approval safety data collection is ongoing. We look forward to working with FDA in creating a robust and effective DTC user fee program as part of PDUFA V.

Let me talk about patient reporting

of adverse events. While we commend the FDA for working in PDUFA IV on improving the assistance whereby consumers can report their problems with medical products, there is much room for improvement. If FDA wants to encourage voluntary consumer reporting of adverse events, the agency must work harder to ensure that these mechanisms are consumer friendly.

We have concerns, for example, about the ease of consumer reporting under the MedWatch online voluntary system. If you go online and try to report on MedWatch, Form 3500, the first thing you're asked is to provide a patient identifier. What is this? We have discouraged consumers from sharing information including Social Security numbers. I know you don't want Social Security numbers but I think consumers are asking themselves what is this number that the MedWatch system is seeking. If this is the first piece of information asked for consumers, they may be

stopped in their tracks and not fill out the form. We feel really strongly that in order to get consumer buy-in you have to make the form as simple and easy to use as possible. Also when people are reporting adverse events, we have to be sensitive to the fact that they might be managing a serious medical condition. Therefore, it's all that much more important that we make the process user friendly. In addition, all DT ads, including those on the internet, should include information on how to report an adverse event.

Let me speak briefly about off-label issues. NCL supports the comments of our consumer colleagues on this issue. PDUFA V presents an opportunity for the FDA to address some of the issues around off-label use to ensure that they are safe and appropriate and that the consumer is informed.

Many consumers are likely unaware that they are even being prescribed off-label drugs. A Wall Street Journal poll found that

about half of Americans thought that a medication should only be prescribed for the disease for which it had been approved demonstrating a consumer lack of understanding of the current process. Do consumers appreciate that such a thing exist as off-label prescription? Do they have any idea how common it is?

Consumers should be informed about the following if they are prescribed off-label drugs; the availability of any indicated alternatives, a body of evidence that supports the products used for off-label, the duration and level of experience with the proposed indication, special population considerations, approval and status and use in other countries, and implications for insurance coverage.

We urge that under PDUFA a specific fund be directed to examine the safety of off-label prescribing the implications of consumer lack of awareness and understanding

of the practice.

Two additional points. NCL has a seat on the FDA's Risk Communication Advisory Committee which is working to streamline and add clarity to the FDA's communications about risks.

The committee, which is made up of academics, doctors, nurses, educators, health marketing specialists and consumer representatives is developing recommendations for best practices in communicating risk effectively. We urge the FDA to pay close attention to those recommendations when the Commission makes it reports which will come out in a series of different recommendations.

Secondly, NCL has petitioned the FDA. We did so in June of 2008 asking the agency to streamline the information consumers receive when they pick up a prescription much of which is in the many pages of information that is currently FDA mandated but nearly impossible for the average consumer to digest.

NCL believes that it makes more sense to provide a single clear patient friendly document that will consolidate the many pages now in use and replace them with one that is easy to read in plain language in a consistent format with plain instructions informing patients where they can reliably obtain information. We welcome and appreciate the agency's input and assessment of our petition.

With that I will close my remarks and look forward to any questions or responses. Thank you very much.

FACILITATOR TOIGO: Thank you, Sally. We appreciate consumer's interest in our drug information.

Diana, you will be the last presenter.

DR. ZUCKERMAN: I'm Dr. Diana Zuckerman. I'm president of the National Research Center for Women and Families and I'm here speaking on behalf of the center and on

behalf of our Cancer Prevention and Treatment Fund.

I should just start out by saying our center is dedicated to improving the health and safety of adults and children and we do that by scrutinizing research and explaining what the research does and does not tell us about medical products and procedures and programs and policies.

Technically we are not a consumer group but we work very closely with the other groups that are represented on this panel and delighted to be here. Really we are a public health group so our perspective is just a little bit different because we are looking more at the scientific evidence.

Starting from that premise I would echo my colleagues in saying that it is very important that consumer voices and patient voices and public health voices be heard as part of the PDUFA process. Let's face it, there's a world of difference between being at

the table and reading the minutes.

So, we can ask to read the minutes. We can ask for access to the minutes. We can even ask for tapes of the meetings but there is a very large difference between being there and part of the process and reading about it later. I do ask the FDA to include our voices and our participation as much as possible and as early as possible. I thank the FDA for starting that process by inviting us to be here today.

I had hoped to do a little bit of consolidation of everybody's views but the one thing about our patient consumer and public health coalition members is that we all speak our own minds and we all make our own analyses. There is no staff for the coalition.

We are an informal group in that we examine each individual issue separately and sign on to statements and letters only when we believe from our own analysis that we agree

with those statements. I'm going to do my best to consolidate some of these ideas but also add some of my own.

I want to start by talking about direct to consumer advertising. You have heard, and I think we all know, that the idea of having a voluntary system where companies could pay to have their ads reviewed before they showed them was not a success. I feel a little bit like Claude Raines in Casablanca being shocked, shocked, that companies would not want to pay to have their ads reviewed and then told what to do prior to doing it.

Let's be clear on these things. This voluntary system has not worked. We need to look at it a different way. We have to remember that there is a purpose of advertising and the purpose of advertising is not to educate consumers specifically, although that can happen through ads.

If that was really the goal there would be a lot better information about risk

as part of that education process. The purpose of advertising is to sell products, whether it's pizza or medication. We need to really be realistic about what the purpose is and how to make sure that those ads are not misleading.

I wanted to say a couple of things about that. We are very pleased that the FDA recently came out with an announcement in the Federal Register about changes that they want to make to direct to consumer advertising. They asked for public comments. We will certainly be doing that.

It has been ridiculous that over the years so much risk information was spoken very quickly on ads either on TV or radio or in tiny fonts that nobody could possibly read even if they wanted to in magazine or newspaper ads or other written ads. The rules have changed and they have improved over the years but not enough.

I continue to see on TV ads

statements such as for more information see this month's Ladies Home Journal. For those of us who don't read the Ladies Home Journal or don't remember which month's issue they are talking about, that is not really helpful information.

Or information like, for more information see our website. Again, a lot of people taking a lot of medication are not web savvy, particularly elderly people. If we want to provide risk information it has to be right there and it has to be clear and it has to be easy to follow.

That reminds me of other little tricks that I've seen lately on ads for Seroquel and Yaz where you have words coming out that are completely different from words on the screen being shown at exactly the same time.

Honestly I don't think you need a Ph.D. in psychology to know but, in case you do, let me tell you that if you look there is

a whole research literature on when the words that you hear are inconsistent with the words that you see, you don't understand them.

One has to assume that since companies that spend a lot of money on these ads are very smart and know what they're doing, they are intentionally showing words that are completely different from what people are hearing and the purpose of doing that is to confuse the viewer or the listener so that they can't follow that risk information message.

You have also heard, as we all know, that by the time the FDA determines whether an ad campaign is misleading, it has already been seen by thousands if not millions of people. The sales have already been made. It's too late to make much of a difference and that has to change.

We need user fees that the FDA can use to review ads in a timely manner that should be prior to the ad campaign being

shown. If that can't be done, then it should be immediately after the ad campaign starts. To do that FDA needs more resources.

As part of the Federal Register announcement the FDA said that they wanted to be flexible. They didn't want to have clear-cut exact rules about companies can do this or can't do that on certain kinds of presentations of risk information.

I'm all for flexibility but flexibility requires more resources. If every single ad has to be reviewed in every way because there are no specific rules about, for example, the words on the screen have to be the same as the words being spoken at the same time, or, no, you can't have distracting noises and distracting movements on a TV ad at the time you are given risk information.

If there are no strict rules, then the resources that FDA is going to need to review them and the resources they are going to need to negotiate when companies push back

after the FDA doesn't like something, those resources are going to be much more extensive.

If that is the decision that FDA makes, then those user fees have to be larger and they can't just be sliding fee scale if that kind of flexibility is wanted by industry. It seems to me those decisions have to be made. You have more flexibility. You need more resources. If you have less flexibility, maybe you won't need quite as many resources.

Last time as part of PDUFA IV many of us up here and other groups that we've worked with in the Patient Consumer and Public Health Coalition asked for a two-year delay in advertising before direct to consumer ads could be used. The purpose of that was that during those two years we would learn a lot more about the product. Obviously these products are studied on relatively small numbers of people for relatively short periods of time. Then they are used by millions of

consumers and some of them are being harmed. We still agree with that two-year delay and we think it's very important.

In addition, if companies are being required to do post-market studies because the initial studies didn't answer all the questions about safety and effectiveness, that needs help from user fees, too. In the ideal world the appropriations would pay for all of this. In the real world that doesn't happen. I don't think it's enough to use part of the regular PDUFA fees for post-market studies and post-market resources from the FDA.

Either those fees have to be much larger for all companies or there has to be separate post-market fees for those products that have not proven that their product is safe and effective sufficiently and, therefore, post-market studies are done. It would be fair if those studies that did not provide adequate information paid more fees for that post-market work.

I want to also talk about agreeing with other members about comparison studies and how important it is that the FDA demand that new products be compared actually both to placebo and to other products on the market. Comparative effectiveness research has the potential of helping many, many patients and consumers by providing information that they truly need, and physicians, too, of course, and other providers, information that they truly need to make the best decisions about what products are best for which people under what circumstances. I also want to emphasize that sometimes we are having products enter the market where their effectiveness against placebo is not clear. They may be as effective as other products on the market but not statistically significantly more effective than placebo. I think nowhere are those kind of issues more important than for antidepressants where you have a lot of products that are only slightly better than

placebo only under certain circumstances so it's very important that we have data to compare to each other. Again, if that requires more user fees as well as more appropriations to make that happen, it's very important that it happen.

So, in conclusion, I just want to say that patient consumer and public health groups like ours appreciate being part of this PDUFA process. We don't necessarily have to be there to negotiate the details of the fees but if PDUFA is going to go beyond the idea of companies providing user fees to speed up the process and if instead of just speeding up the process we also want to make sure that these products are safe and effective for the people using them, then our voices need to be part of that process so that speed is important.

We want products to be brought to market as soon as possible but we want them to be truly safe and truly effective and if they can't be safe and effective for everyone --

and many products can't be -- we need more information about who they are effective for, under what circumstances, and PDUFA can help improve that situation and I hope that it will. Thanks very much.

FACILITATOR TOIGO: Thank you, Diana.

Are there any clarifying questions from our steering committee for any of our consumer panel? Okay. Well, then, thank you, Bill, Kim, Sally, and Diana. I'm sure we'll be seeing you much over the next six to nine months and we appreciate you providing the consumer perspective as we begin the next PDUFA process.

With that, we are early for our break so if everybody could be back at 11:00. Coffee you are on your own for. It's available in the hotel but it's available for cost. We will see you back at 11:00. Thank you.

(Whereupon, at 10:34 a.m. off the

record until 11:02 a.m.)

FACILITATOR TOIGO: Okay. We are going to get started with our next panel and that is Panel 3, the patient perspectives. Like before, we are not going to read bios. You can look at those for what was at the handout table and people will discuss the organizations they represent as they begin speaking.

We have four speakers. Diane Dorman from NORD, Mark Boutin from the National Health Council, Dan Perry from the Alliance for Aging Research, and Ellen Segal from the Friends of Cancer Research. We have three presentations and Ellen in her presentation will be using slides. We'll start with Diane.

MS. DORMAN: Thank you, Terry. Thank you very, very much. As Terry said, I'm Diane Dorman, Vice President for Public Policy for the National Organization for Rare Disorders. NORD represents the 30 million

men, women, and children in the United States that are affected by the approximate, I think the number is around 7,000 known rare disease.

For those who may not know, a rare disease is defined as any disease, syndrome, or disorder that affects fewer than 200,000 people in the United States. For most of these 7,000 rare diseases, the populations are far smaller, sometimes 15 to 20 people in the United States.

Development of therapies for rare diseases poses a significant series of challenges. One of the main challenges, of course, is financing. Rare and neglected diseases, by definition, have a small target patient population and the investment needed to develop a new drug is substantial and carries a high risk of failure as does all drug development.

Other challenges involve the drug development process itself. All drug development starts with the identification of

a substance that may have some therapeutic affect against disease. The process continues with the production of the substance in a form that can be used for medical treatment, study in animals and humans, and finally compilation of the data for registration purposes.

All along the pathway, drugs being developed for any disease face enormous challenges and risks but this is even more so for products intended for rare and neglected diseases given the small patient populations, the frequent lack of disease progression data, and the scarcity of medical specialists.

Congress has recognized the unique challenges posed by the development of orphan products. The Orphan Drug Act of 1983, for example, provides financial and exclusivity incentives for orphan drug development to encourage companies to develop such drugs. That law has been successful in encouraging development and approval of approximately 350 orphan drugs.

In order to further the development of orphan drugs, biologics, and humanitarian use devices, NORD believes PDUFA V with the support of the FDA may help NORD and the entire rare disease community identify and implement a new pathway to orphan product development. There are a number of questions that we need to answer.

How do we advance new rare disease uses for drugs approved for other uses? How do we help accelerate existing rare disease programs? How do we design and evaluate studies of drugs intended for diseases with small patient populations? How do we use surrogate markers with more confidence to hasten the availability of more treatments for rare and neglected diseases? How do we organize government programs to facilitate the development of orphan products?

NORD views PDUFA V as a unique opportunity to develop a comprehensive series of recommendations to advance orphan product

development. NORD strongly believes that engaging Congress and FDA officials in the process will lead to practical, detailed recommendations that can be implemented throughout the development process.

Now, I would like to talk very briefly about advisory committees and the conflict of interest. During FDAAA negotiations NORD argued that because patient populations are very small few companies are willing to take on the financial risk of development orphan products and there are few researchers conducting this research.

Identifying experts not financially conflicted to sit on an advisory committee is, therefore, very challenging. Unfortunately, our concerns were not addressed in FDAAA and our worst fears were realized.

Consideration of a life-saving therapy for the treatment of infantile spasms was delayed for consideration in 2008 for six months simply because an expert could not be

identified who was not financially conflicted.

Without treatment, infants and children unable to receive triton because of infantile spasms experience profound brain damage and sometimes death. Although we recognize that conflict of interest issues continue to be a concern, it must be addressed. Orphan drugs and biologics are very unique and must be dealt with differently.

These delays will occur again and again until Congress and the FDA recognize that orphan drugs, biologics, and humanitarian use devices are unique and must be addressed differently. NORD along with our medical advisory committee continues to look forward to work with the FDA to identify experts in rare diseases.

I would also like to speak very briefly about the off-label use. As I mentioned earlier, there are about 350 orphan products, some not on the market and some

continue to be on the market, that treat only about 200 rare diseases.

Now, if you do the math and there are about 7,000 non-rare diseases, that means that about 68,000 rare diseases have no treatment specific to their disease. As a consequence, they are treated off-label. Eighty percent of the people in the rare disease community are treated off-label because those 350 products do not treat their very rare disease for a very small patient population.

I also would like to make mention, too, that I note there is a great deal of concern about risk and safety. We realize that is extremely important because people with rare diseases also want to make sure that the products they take are safe and effective. However, people with rare diseases are willing to take on a far greater degree of risk than patients with a headache or arthritis simply because there is no therapy

available for them.

I want to thank the Food and Drug Administration for this opportunity. We look forward to working with the FDA and everyone else in the rare disease community to ensure that the agency continues to explore new avenues for the development of new and innovative therapies for the treatment of rare diseases.

The formation of the Office of Orphan Drugs headed by Dr. Anne Pariser is an excellent step forward and we congratulate the FDA for this move forward. Thank you.

FACILITATOR TOIGO: Thank you, Diane.

Next on this panel is Mark Boutin from the National Health Council is going to be next.

MR. BOUTIN: Thank you, Terry. As you heard, my name is Mark Boutin. I'm with the National Health Council which is an umbrella organization of patient advocacy

organizations. We provide a united voice for people with chronic diseases and disabilities.

Our membership includes 50 of the leading patient advocacy organizations such as the American Cancer Society, American Heart Association, as well as many other patient advocacy organizations. We also include other membership categories and they include member organizations like the Association of American Cardiologists, as well as nonprofit organizations that deal with family caregiving and business and industry.

Our governance is controlled by our patient advocacy organization but we seek to provide a place where all stakeholders can come and have meaningful and recent dialogue.

I want to say that the National Health Council represents patients, not consumers. I want to make the distinction because you just saw a panel of consumers and now you got to hear from a panel representing patients. Our perspectives will appear to be

almost the opposite in some respects, yet we represent many of the same issues.

It creates a challenge. I would say to you that the issue is not that we don't have a lot of concerns in common. The issue is that our focus is entirely different. People with chronic diseases and disabilities use our health care system to manage their daily lives. They use the health care system to stay alive. Many of these people will die still utilizing the health care system on a continual basis.

Consumers are people that use the health care system largely on an ad hoc basis so their perceptions on these issues, their focus is often very different. From the patient perspective, we have been involved in this issue largely because we want treatments to be brought to us quickly.

We are obviously concerned about safety and efficacy and that needs to be maintained but we want to speed up the process

of getting new treatments to people with chronic conditions. Especially people with chronic conditions that have no viable treatments or the treatments are simply not sufficient to sustain them over the long term.

I also want to remind this audience that, before PDUFA, it was the patient community that stood up and said, "Enough is enough. You need to do better." You only have to look to the '80s and the HIV and AIDS crisis where the patient community aid, "This is not working. You need to speed this up. We are dying and we need treatment and we need them now." And as a result you saw dramatic results. You saw a population that had one treatment that was very hard to tolerate, eventually have multiple treatments. Just recently, you saw a new drug put on the market that works in a very different way that for many people who were having difficulty on the existing drugs now can take this drug, give a test through a biomarker and ensures that it's

safe and effective for that population. They receive this drug and it's had amazing results with almost no side effects. That population was heard. We saw some advances in the cancer community and some advances with heart disease. The reality is we are still not getting treatment as quickly as we, in the patient advocacy community, would like. We have been supportive of PDUFA, and certainly when you look at previous iterations of the PDUFA authorization and process, we have seen great results in speeding up new products to market and still maintaining the safety and efficacy.

Our challenge has been that over previous models with additional resources we have actually been able to realize some efficiencies. We have seen dramatic results, especially in PDUFA I, II, and III. I would suggest to you, in this last go-around, we are not seeing the same efficiencies. In fact, we are seeing some challenges from the patient

perspective. We are not getting the treatments nearly as fast.

That leads us to two very broad recommendations and then some specific recommendations. The first very broad recommendation, and you've heard this from a consumer perspective and we will join them, you need to have patient involvement at all levels throughout the FDA and within the discussion of what is going to be in PDUFA V. It is critically important that the patient perspective be there.

Patients are their own experts. You can't underestimate the knowledge that an informed patient has about their condition. In fact, if you have a rare disorder, you probably know more about your condition than any of the providers you are seeing.

We are very knowledgeable about what is going on in our conditions and there is nothing more informed than a patient who has been diagnosed with a serious life-

threatening disease or disability.

Perhaps even more importantly, we provide credibility to the process. Right now, we are in an age of transparency. We want everything out in the open. We have already heard a call for the PDUFA agreement to be negotiated in the OPEC. The reality is you need patient involvement to ensure credibility of the outcomes.

The reality is we are making tremendously difficult decisions about benefit and risk. The patient needs to be a part of that conversation and we can give you the credibility when you make tough decisions because we know there is going to be risk.

As has been stated earlier, people with chronic conditions understand that all medications have risks. Often consumers do not. That creates an opportunity for education and learning but for the people who are taking medications on a daily basis, they understand that there is a risk associated

with that but they are willing to take that risk at a shot of a more normal, productive and happy life.

Too often the decisions about benefit and risk are made by people who are healthy, who are not taking a medication. They have a very different perspective in this space. So include people with chronic conditions, patients in all of the decision making including the risk evaluation mitigation strategies.

There are three very specific recommendations in this place. Again, include us in all safety considerations including the REM process. Any data collection that is required as part of a REM strategy or any other mechanism needs to account for the benefits as well as the risk because it's only when you combine the two and frame them in the context of the condition being treated or conditions being treated can you make any effective judgment about benefit and risk.

Third, and this speaks to our concern over PDUFA IV which, as we've heard throughout the day, really focused in on new safety mechanisms. We, in the patient community, support safety and efficacy mechanisms but we do not want it to impede the speed at which we get new treatments, especially for conditions without treatments.

When you look at these issues from a patient perspective, we are seeing less treatments come out and it's creating a lot of concern and anxiety. I will tell you that the patient advocacy community worked hard on the last PDUFA reauthorization to change the language in the REM strategy. Specifically because we wanted the safety and efficacy mechanisms to be in place. We wanted it to be used as a tool in post-market surveillance to ensure safety but to speed the process of getting the drug to the populations who needed them before you could figure out every single risk in a clinical trial process. It's our

assessment that has not worked. We call for the Government Accountability Office to conduct an assessment and analyze the impact of safety considerations including the REMS process on patient access to new drugs. Again, we are not saying that we do not want additional measures for safety and efficacy but they should not be impeding access to drugs because, remember, so many people with chronic conditions are living and dying as a result of their condition, waiting for treatment.

My second over-arching recommendation, and this may be a bit perplexing to some and I'll explain it, but the next PDUFA needs to encourage the development of innovative trial designs that speed the delivery of new and effective treatments to market. There are some that will say, "Well, PDUFA is a user fee agreement. It's simply for the approval of the drug in the existing process."

I say to you, no, it is not. The patient community came out and we demanded change for HIV and for certain cancer treatments. We supported PDUFA because it streamlined the process. It made it more efficiency and we got products to us more quickly. The reality is many of those efficiencies have been accomplished.

Our next opportunity is to figure out how to develop trials that streamline the process, that target the population it is going to reach. We have tremendous opportunity here. For the first time in my professional advocacy career we are seeing Japan, and to some extent Europe, outpace us in this.

That makes no sense to me as a patient advocate. We need to do better in that space. To that extent, I have three specific recommendations. We need new methodologies for conducting non-inferiority trials. We need trial protocols for specific

therapeutic areas. Perhaps most important from a patient perspective, we need biomarker and surrogate endpoint qualification.

We need to figure out how to do this in a very predictive way. We need to allow industry to go into this space. We need to figure out how to define our population we are going to provide treatments to make them safe and efficacious. We need to speed this up and we need to reduce the cost and burden of developing these trials.

We also need to ease the restrictions on FDA with data. We need to encourage research for potential biomarkers and we need to track clinical trials that have been discontinued from the trial registry. We see a lot of opportunity in this phase to raise all boats, so to speak, and seek opportunities to develop meaningful treatments more quickly and obviate potential harm.

I'm going to close by saying just this. You need to understand that the patient

community is getting really frustrated, frustrated at a level that I haven't seen in a long time. The patient advocacy community worked hard to double the funding for NIH. It was where we cut our teeth in advocacy.

We expected a commensurate gain in the development of new treatments, and yet we know in the last decade we have more than doubled our investment in new treatments through public and private funding. Yet, the realization has been that we are getting less treatments than we did.

The patient advocacy community is getting angry. It has become clear to us the challenges are at the back end of the process. We need to do better in getting new treatments through FDA in more efficient structures that provide treatments to the people that need them.

The AIDS epidemic proved that we can do this and I suggest to you why should somebody with lupus or somebody with ALS, Lou

Gehrig's disease, or Alzheimer's or Parkinson's or lung cancer, why are they not getting the treatments that they need? Why are they still dying?

On behalf of the National Health Council, I urge you, again, adopt a more balanced framework for benefit risk assessment, ensure that patient participation is there. We will help you make those tough decisions. We accept the risk. We understand the risk of our conditions.

Second, it's time to improve the regulatory science that speeds the delivery of new safe and effective treatments through innovative trial designs. Thank you for your time.

(Applause.)

FACILITATOR TOIGO: Thank you, Mark. And as one who has long been trying to champion FDA including patient perspective in our process, I thank you for that and I think we certainly have made a lot of progress since

the HIV epidemic. I would encourage you to tell the pharmaceutical industry to include patients in all phases of their process as well. And that way we truly will have patient perspectives included. So, thank you.

Dan will be our third presenter for this panel. Dan Perry from the Alliance for Aging Research.

MR. PERRY: Thank you very much, Terry. I appreciate having this opportunity to offer some comments on the Prescription Drug User Fee Act and the current experience with PDUFA IV. As you have heard, I am speaking today on behalf of the Alliance for Aging Research.

The Alliance is a not-for-profit organization established in 1986 to advocate for public policies that will promote medical and scientific advances in understanding human aging and its relationship to a large list, long list of chronic diseases that afflict older Americans, with our goal being to

improve the quality of life and survival for people as they grow older.

I want to first begin by thanking the employees of the Food and Drug Administration for the tremendously challenging and important jobs that they do every day, and especially those of you representing the FDA who are here. The work that you do truly impacts the lives of millions.

Well, we are all familiar by now with the rapid and consequential aging of populations throughout the developed world. Beginning this coming January first the leading edge of some 77 million American baby boomers, the largest age cohort in our history, will begin to turn age 65 and will move onto the nation's Medicare rolls.

Very soon the U.S. population will go from the current state of about 6,000 people a day turning age 65 to very soon from 6,000 a day to 10,000 a day and it will stay

at that level for the next 18 years. That's the weight and the duration of the post-World War II boom.

We also know that as people grow older they will experience increasing risk to a long list of age-associated chronic ailments. Coronary artery disease, stroke, heart failure, type 2 diabetes, bone and joint disabilities, cancer, clinical depression, vision and hearing loss and neurological declines from diseases such as Alzheimer's and Parkinson's, and that's just to name a few.

Clearly unless we find better and more effective ways to prevent, postpone, and reduce the impact of these diseases of aging, the U.S. will experience a crushing wave of disability and lost potential that will carry enormous cultural and economic consequences.

At the Alliance for Aging Research we view the federal agencies that monitor public health and that advanced medical research and regulatory science -- these are

America's most important defenses as we face what we call the silver tsunami.

We believe that FDA's processes through which new therapies are reviewed and approved are critical to ensuring the continued translation of basic science discoveries into therapies that older patients and their families so desperately need.

For the past four years the Alliance for Aging Research has chaired a coalition of more than 50 national nonprofit groups to focus on one disease of aging in particular and that's Alzheimer's. This is the ACT AD Coalition and that stands for Accelerate Cure and Treatments for Alzheimer's Disease. It's a coalition comprised of dozens of prominent organizations representing the interests of Alzheimer's patients, seniors, consumers, women's health advocates, caregivers, health care providers and researchers.

The coalition is working with the

nation's leading Alzheimer's researchers, clinical trialists, drug developers, as well as the FDA to take a closer look at some of the hurdles that exist as new Alzheimer's therapies are developed, tested, reviewed, and eventually brought to market.

Through this one effort several challenging issues have come to light that are implicated in the scant number of Alzheimer's treatments available on the market. And currently there is no available drug that will actually modify the course of the disease. What we currently have are five products that provide temporary relief of symptoms for some patients and that is simply not adequate for the future.

Alzheimer's currently afflicts some 5.2 million Americans. That includes half of all Americans over the age of 85 and half of all of those in nursing homes. By 2030 when even the youngest member of the baby boom generation will be at least 65 years of age,

these already intolerable numbers will triple.

The financial and social burden of this disease are breathtaking. Five years ago Medicare spent $91 billion a year on this disease. In another five years the cost to Medicare will more than double to 189 billion and in 25 years Medicare will be spending as much on Alzheimer's as it currently does on everything else today.

Our only hope is to make discoveries in the lab that will bear out in clinical trials and lead to better means to prevent, postpone or reduce the devastating impact of this disease. Much of our coalition's work on this disease focuses on how to select patients for clinical trials, testing treatments that can intervene in the earliest stages of the disease, how to appropriately balance the benefits of the potential therapies against the ever-present risk of harm from the treatment.

How to generalize the results in a

specific trial population to the larger patient population. And most importantly, how to measure the clinical benefit of treatments for patients at the earliest discernible stages of the disease.

The Alliance for Aging Research and the ACT AD Coalition look forward to continuing to engage the FDA on ways to optimally design clinical trials for Alzheimer's disease. This then represents the context in which we view the Prescription Drug User Fee Act and PDUFA IV in particular.

We applaud the FDA's commitment under PDUFA IV to increase stakeholder involvement in discussions surrounding the advancement of science and the development of clinical treatments to help overcome roadblocks that otherwise might slow down the development of new therapies for a host of diseases.

We are pleased to see the inclusion of pre-market review enhancements specifically

targeted to expedite drug development. Guidance on topics such as adaptive and enriched clinical trial designs is important not only for Alzheimer's disease but also for all of the other diseases that face us as we grow older.

Guidance on the qualification of biomarkers for use in drug development for age-related diseases will positively impact patients by informing decisions on treatment's efficacy and safety while reducing the time and improving the efficiency of bringing the therapy to market.

Ongoing public exchanges with all parties interested in making more meaningful treatment options available to patients who need them are something we hope to see continue as the agency moves forward with PDUFA V guidelines.

The Alliance for Aging Research supports the approach in PDUFA IV to address the risks and benefits of treatments in a

post-market environment. We believe this life cycle approach to drug evaluation will allow better access to treatments for patients who need them and a faster response in identifying and reducing risk or harm.

All drugs come with risks but we believe that when physicians and patients are presented with the best available information, patients, particularly those with little or no therapeutic options for life-threatening diseases, are best able to determine what level of risk they are willing to accept.

We know that new mandates placed on the FDA under PDUFA IV for enhanced post-market safety surveillance require rapid development of systems capable of active risk identification and analysis. These also increase the workforce demands on FDA staff.

These responsibilities were placed on the agency at a time when FDA's own science board had identified the agency's IT infrastructure as inadequate for its current

operations. So we hope that once FDA's five-year drug safety plan is fully implemented and new staff fully trained in these areas, the new PDUFA IV mandates will become less of a strain on the agency and not contribute to problematic delays in bringing therapies to market.

Finally, the Alliance for Aging Research recognizes the critical importance of user fees funding currently provided to the FDA. For the last four years we have served on the board of the Alliance for a Stronger FDA. This is a diverse and a very effective coalition committed to increasing the resources necessary for the FDA to carry out its ever-expanding responsibilities.

The user fee established has been successful in meeting the initial goals of reducing application backlogs and ensuring that important therapies become available to patients sooner by enabling FDA to hire more staff, improve systems and better manage drug

review processes.

User fees are properly limited to their scope and cannot be used to cover many of the increasing costs the agency sees each year. Therefore, user fees do not offer flexibility for the agency to adopt initiatives that could increase its capacity to modernize as science and technology evolve.

There are ways in which FDA can facilitate biomedical innovation such as adopting more modern preclinical testing methods but these can only be realized if the agency has the ability to allocate funds where they are most needed. This cannot be achieved through user fees alone.

Therefore, our organization and others will actively continue to call on Congress to provide appropriate funding to the agency so that it can play a leading role and a proactive role in improving the health of aging Americans.

Thank you for the opportunity to

share these comments on PDUFA and the current PDUFA IV process. I welcome the opportunity to provide additional information as the PDUFA V process moves ahead. We look forward to working with the agency in order to move needed treatments for patients and their families in a safe and efficacious manner.

FACILITATOR TOIGO: Thank you, Dan.

Our next speaker is Dr. Ellen Sigal from Friends of Cancer Research.

DR. SIGAL: Thank you, Terry. I'm sorry. We are so used to slides. We're just used to wonky presentations and you wouldn't dare get up without slides.

I want to also thank my fellow panelists. I agree with things that were being said and I want to endorse it. Friends is a think tank for cancer research science policy. Our board consists of the American Cancer Society, ASKO, which are all the clinical oncologists, scientists and clinicians, all the cancer center's patient

groups and others so we are pretty diverse.

I want to start with something that is incredibly important and that is the patient because this is all about the patient. What you do at FDA is about the patient. What we do, what we care about ultimately, it's not for the companies, it's not for FDA. It's for the patient.

What do they want? Well, they want clear information on benefit risk for them, for their disease, for their disease state. That is important information, understanding that this is evolving and we don't know it all.

The other thing is we know, particularly when new drugs are approved, and particularly for indications like cancer, we don't know all the risks but it is incredibly important to understand the risks as they evolve and to have that continuum of a process going on.

There isn't one size fits all for

patients. We are old and young. We have different states of disease. We have different states of what we can tolerate and the knowledge that you cannot put cancer where perhaps 200 diseases.

If you look at pancreatic cancer, late stage disease with an imminent death threat, your risk tolerance will be very different than for early-stage 30-year-old woman for breast cancer. If you are using adjuvant therapy or once you start getting into the world of chemo and prevention for high-risk women, it's going to be very different.

So it's very important to understand that risk is very personal and as we understand personalized medicine and our personal risks it's going to be very important to take that into consideration, so anybody who says they speak for all patients knows, as my colleagues know, that we are very different.

The other thing is that we understand that we have to work in the world that is but that is the very beginning. We can't really serve patients without innovation. For many, many years at Friends we only concentrated on the NIH. We worked to increase the budget. We worked with all of my friends and colleagues and felt that was the most important thing. And in fact, it's extremely important.

On the other hand, ultimately the work of discovery has to be translated to patients so what patients need and what the agency does with that information is incredibly important.

We had enormous outcomes from PDUFA IV. Certainly REMS program, post- marketing data, development to improve clinical trial registry. All of these things were important. It's evolving and we support the changes that were made, although we need to really look back and see how useful they are and how to

expand them.

PDUFA V is the beginning. We have almost two years and we need to really think about what is best on that. I'm happy that the agency is starting early because I think it is important to really think about that and integrate the changes that were made and to think wholly about what we need to do.

We have to improve upon processes that were started. Some of them, you know, it took a long time once we passed it, just like health care reform, to understand what we have so we do need to evaluate and we need to continue to make them better so they are more meaningful.

Safety is really important. It's important to all of us just like disease is important and benefit. So the idea of OND and OSE -- I'm going to talk in the FDA acronyms -- they should work, they should work together, they should be transparent and they should include the voice of patients. It's extremely

important because it's patients that have the disease. It's patients that have the expertise. The voice of the patient is extremely important. They cannot be done in isolation because when you look at the way trials, particularly in cancer, are, in Phase 1, it's a very, very small population. We will not have all the data. Again, the risk of patients who are diagnosed with cancer or other diseases may depend on the stage of their disease and what they are going through and their co-morbid conditions.

FDA needs the expert personnel to really make these informed decisions. The pace of science is staggering. The requirements, the knowledge of what really works or doesn't work is incredibly important. FDA has to recruit the best possible people and they have to pay them.

They have to pay them scales that are commensurate with what we see in academic sectors and other places. I know there was

some relief a little bit more on payment mechanisms but if you don't pay people the right salary, they cannot do this job so it's very important that your pay scales are competitive with the NIH and with other government groups. You have to really look at your Title 42 and see that you can recruit the best and the most trained people and they have to be paid.

There is a lot that was done on post-market surveillance, the OMOP program, the Sentinel program. There are some very nice outcomes. We need to really build on it. I think the advantage of the OMOP is we have the ability of all parties working together on it. It's about ready to come to closure and we now really have to look at the Sentinel.

The importance of the OMOP is that they had patients and they had industry and others working on it so Sentinel needs to be done. It needs to be done properly. It needs to have the right technology and the right

input. These are going to be very important issues that we are going to look at going forward.

The reauthorization is a three-legged stool. You cannot do this, just the PDUFA fees, without looking at the needs of the entire agency. It is disproportionate. It won't work. I don't care what you do. If the fees are 90 percent, it won't work. You really have to have a science base at the agency and you have to really look at the systems. You have to look at the technology and you have to look at the entire agency. Looking at one portion of it without getting commitments for regulatory science, without getting commitments for increased technology, increased functions it won't work. We are very much at the beginning of PDUFA but I can tell you we are going to be stressing the needs of the entire agency and not looking at PDUFA in isolation because it really doesn't work. If the agency is underfunded and it's

going to be very, very important to really look at the needs of the entire agency.

There is an enormous amount of data that the agency has for completed clinical trials. Enormous. We would like to see that tracked with NIH registries. We would like that data to be really meaningful because right now they have this data and they can't do a lot with it.

Recently we worked with the FDA and the NCI or the NIH and others to form the interagency agreement between the FDA and the NIH. We think this is an important start. I think there is a lot that can be done with trusted sister agencies and we really think this should be expanded, it should be prioritized, and they should think about what they want to do with that, whether it's adaptive trial design, biomarker validation. There is a lot of science at the NIH and we applaud that.

Public/private partnerships. At

Reagan-Udall, at the PDUFA V, we did get Reagan-Udall authorized. We never got it appropriated so that is a wonderful opportunity to not do regulatory science but to really do public/private partnerships that would be meaningful and really get information for patients. That would be wonderful and we can do extraordinary projects.

The foundation for the NIH does incredibly important projects. As a matter of fact, OMOP, biomarker consortia have FDA, NIH, CMS at the table so I think the ability to work more with public/private partnerships are incredibly important.

We can also work with academic centers. I think some of the regulatory science as we get it funded can be done through centers and other collaborations. But there is a lot of science out there that we really have to work with.

We think that the external advisory capacity of FDA really needs to be enhanced

and not just drug-specific, because when you are dealing with one drug it's something, but I'm talking about adaptive trial design, biomarkers, new animal models, pain, quality of life. What do we know about that in the regulatory environment?

So the ability to really convene expertise because even fully funding regulatory science, even fully funding these partnerships that evolve with Reagan-Udall, or foundation for NIH, or at the NIH, are insufficient when you are asking very specific questions. The ability to really get the expertise from the community is going to be very, very important because the science today is different. It's different. In cancer, we are a rare disease now. We're not talking about breast cancer. We're not talking about colon cancer. We're talking about KRAS and very sophisticated mechanisms. Our disease is now small patient so the trial design, the safety profile, the animal models, the amount

of data that has to be collected are very, very different so we really have to start to really embrace the science that we have now that will make a much better role.

Basically the PDUFA V goals are bolstering the scientific infrastructure at the agency but not looking at it in isolation. We feel very strongly, have regulatory science components both in PDUFA and outside. It really has to be supported. We have to build on the expertise and decision-making that exist in the agency and other agencies and really fund the agency appropriately because even if they partner with the world, if they don't have the right people at the agency that understands the science or understands the mechanism of disease and understands where the disease models are going, they will not be able to partner equally and effectively with the voice of regulatory science so this is very important. We hope that this will all work and we look

forward to a long and a very interesting conversation.

(Applause.)

FACILITATOR TOIGO: Thank you, Ellen.

Are there any questions from the steering committee for the patient panel? No? Okay. Well, then I thank you all for your thoughtful comments and I look forward to you continuing to work with us as this process moves forward. We'll break for lunch and we'll start back at 1:00.

(Whereupon, at 11:51 a.m. off the record for lunch to reconvene at 1:04 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

1:04 p.m.

FACILITATOR TOIGO: Okay. We're going to get started. And we're on Panel 4 if you're following the agenda. And it's a little bit after 1:00. And we have representatives from four health professional organizations who are going to present.

And one clarification before we get started. Somebody had asked me when I referred to a steering committee as does anyone have question. We actually have a listening panel this afternoon, which is Dr. Jenkins, Dr. Yetter and Dr. Mullin. And so I was referring to them if they had any questions that they wanted to ask our panel members. So just for clarification that you know that.

So we're going to hear from two pharmacy organizations, from the American Medical Association and then we're going to hear from the kids. Mark's going to talk to

us from the American Academy of Pediatrics.

And we're going to go right in the order that they are listed on the agenda with Dr. Marcie Bough as the first presenter.

DR. BOUGH: Good afternoon, everyone.

Again, my name Marcie Bough. I'm the Director of Federal Regulatory Affairs for the American Pharmacists Association here in Washington, D.C. And I'd like to take this opportunity to thank you for letting us present the view of the nation's pharmacists.

APhA is the first established and largest professional pharmacy organization representing over 62,000 members who provide care in all practice settings.

APhA supports the reauthorization of PDUFA and recognizes the need to continue PDUFA fees and source of funding for the FDA in addition to appropriations.

Furthermore, we support continuation of the expanded scope of PDUFA

beyond the initial approval process to further strengthen and improve the program to ensure safety monitoring throughout the life cycle of a drug.

As the health professionals who work closely with patients and their medications everyday, pharmacists rely on FDA to regulate safety of medications.

My comments will focus on the questions posed by the agency for today's discussion on the assessment and ongoing improvements to PDUFA.

FDA question 1: What's your assessment of the overall program of PDUFA IV this far?

APhA appreciates the work that FDA has done to implement PDUFA IV provisions. The agency is meeting goals to increase resources, accelerate the drug evaluation process and improve close market safety surveillance activities. APhA is encouraged by the ongoing efforts to increase staffing,

upgrade HIT infrastructure and electronic reporting processes, increase coordination and collaboration within the agency, and increased communication and outreach to stakeholders. Such efforts are crucial for the agency to meet its mission, to protect the public health and ensure the safety and effectiveness of drugs.

Furthermore, additional FDA funding through both fees and appropriations remain necessary in order for FDA to continue to meet its goals and to address an increasing number of new molecular entities, biologics and pharmacogenomic guided therapies while maintaining a strong focus in quality and safety.

Question 2: What aspects of PDUFA should be retained, changed or improved?

Related to FDA outreach, as I mentioned, FDA has significantly increased the outreach strategy to stakeholders over the last several years. Most notably from the

Office of Special Health Programs and Terry's team. I would like to express APhA's appreciation for FDA's effort to improve these communications and processes for alerting the health care provider organizations, including APhA, on emerging safety issues and announcements concerning FDA regulated products.

Pharmacists are the most successful health care providers to many patients and are often called upon to respond to patient questions based on media and print coverage. Outreach about forthcoming teleconference briefings serve as a valuable tool for alerting stakeholders to FDA advance notices and information to come. However, more can be done.

We encourage FDA to continue strengthening its outreach and communication strategies and to build upon existing partner programs to help distribute information safely, such as the MedWatch Partners program.

This can better utilize partners to further distribute information.

With advance notice and planning, the stronger Partner program can help us stakeholders use FDA information to prepare and distribute safety information and what you need to know information to our members to better prepare their responses to patient questions.

We look forward to ongoing information and collaboration from FDA.

Related to post-market surveillance, APhA supports FDA's implementation of post-market surveillance activities that better allow FDA to monitor safety of the drug throughout its life cycle. Furthermore, we support resources necessary for post-market surveillance that reflect FDA's needs. PDUFA IV provides enhanced opportunities for identifying risk and benefit in real life consumer use of those drugs, and it streamlines the collection processes. Such

efficiencies may also increase front line provider participation in post-market surveillance. Therefore, we encourage the increased utilization of post-market surveillance activities as outlined in the PDUFA IV five year implementation plan.

In addition, pharmacists have demonstrated their active participation in practice-based research networks and post-market surveillance activities produce valuable data about the safety and effectiveness of approve products. As those surveillance systems evolve and electronic reporting efficiencies are improved, APhA encourage FDA to ensure that pharmacists continue to have the opportunity to participate in and have inoperable access to post-market surveillance activities and systems such as the Sentinel system and MedWatch Plus programs.

We also encourage FDA to ensure that surveillance activities have a feedback

loop for providers so that findings from post-market surveillance activities are reported back to the providers. This can further provide an incentive for more providers to report adverse events.

On a related note, as we look to the meaningful use of electronic health records and the utilization of data within those systems, this allows us to have an opportunity to ensure that FDA approved information is included in electronic health record activities within the Department of Health and Human Services so that infrastructures evolve, that information is linking to FDA approved information whether it's related to patient information, REMS or safety reporting activities.

Related to proprietary drug name reviews, we strongly support FDA's effort to increase patient safety and address drug name confusion. We encourage the agency to continue its Drug Naming review program as

outlined in the five year plan.

As the program progresses, we encourage FDA to ensure that look alike and sound alike review processes include handwritten, verbal and electronic drop-down in screen selection menus scenarios as all of these prescribing vehicles contribute to drug name confusion and should be properly evaluated.

Again, related to CMS activities with Medicare and Medicaid, the increased use of electronic prescribing allows another avenue that should be further looked at to ensure patient safety and that confusions are avoided.

Referring to the review of direct-to-consumer advertising, APhA supports FDA's program to review DTC advertising and supports such funding. As the prevalence of DTC advertising continues to grow, review is critical. Therefore, we recommend that all DTC advertising complete a formal review process

within the agency. The subsequent staffing increases, I'm sure, would be needed.

We further recommend that the agency require manufacturers to provide new product information on DTC advertising campaigns to pharmacists and other health care providers prior to information being available in consumer outlets. As stated previously, information ahead of time would allow health providers to better address the information that may be presented from consumers based on media outlet.

Related to personalized medicine, APhA encourages FDA to build on provision related to personalized medicine and continue the direct resources for staff and outreach activities. This is a fast growing field and much education and outreach is needed both on personalized medicine and pharmacogenomics. We encourage FDA to work with partner organizations to help increase awareness and educate practitioners on how pharmacogenomics

and personalized medicine can improve patient safety and outcomes.

In March 2009 APhA convened a workshop. And we are pleased that FDA and DHHS participated in this meeting that looked at integrating pharmacogenomics into prescribing and dispensing practices. As clinical uptake and support builds, there's growing opportunity for collaboration between physicians, laboratories and pharmacists in utilizing pharmacogenomic date for personalize therapies and dosing decisions.

Related to strengthening the risk management in REMS. While I know that many staff at FDA are actively involved in the REMS program and getting activities up and running within FDA, we are encouraged with ongoing efforts to address the many needs that we see as this program evolves.

APhA has been actively involved in many of the REMS discussions with FDA and other stakeholders over the last few years.

APhA supports the efforts to assure patient safety and appropriate and safe use of the medications. We also appreciate that FDA has acknowledged the many important roles that pharmacists and pharmacies played implementing REMS programs and the administrative and work flow challenges that must be addressed for both prescribers and for pharmacists.

APhA's goal is to be a resource for FDA manufacturers in helping REMS programs achieve the intended outcomes without being overly burdensome on the health care system. Unfortunately, many of the current risk management programs have presented challenges for practitioners due to the growing number of REMS and the lack of standardization between the different programs. The silo effect isn't efficient in practice.

To better ensure success we must learn from the past and use PDUFA reauthorization as a vehicle to improve the REMS program given that FDAAA and PDUFA IV

authorized REMS.

Specifically, as FDA continues to implement its plan to identify, develop and validate REMS elements as outlined in the five year plan, APhA recommends that FDA improve the REMS program by ensuring that manufacturing and FDA receive input from front line pharmacists, physicians and other prescribers early in the development of any REMS. Such input would better ensure that a workable and practical program is being designed.

We also encourage that manufacturers are made aware earlier in the drug approval process if a REMS is going to be required. The earlier a manufacturer knows of a REMS that will be required, the more time they have to gather input from the health care providers.

We also encourage assurance that a standardized system-based approach is utilized that can be applicable to any REMS programs.

That existing technologies, infrastructure and standardized components are utilized that can be streamlined and implemented into prescriber and pharmacist's work flows. That any willing provider has the opportunity to participate. That standardized components are proven to be effective in mitigating the defined risks and are workable for all stakeholders.

We also encourage insurance that outcomes metrics capture the reason for patient success and/or failure rather than just documenting the occurrence.

We encourage REMS programs to be pilot tested.

And we also encourage organization of REMS programs based on levels of intensity to be considered. My example for this is basing it on something similar to schedules of controlled substances.

The last recommendation for REMS is that FDA ensure that the potential impact of pharmacist provided clinical care such as

medication therapy management and improving patient safety as an element of a REMS is recognized in the addition to the need for a viable business model for implementing a REMS requirement of such.

And finally, my last note, we support FDA's ongoing efforts to improve the Medication Guide, patient information, consumer medication information activities that have been ongoing for several years. We know that FDA's well on its way to assuring that we have a new and approved Medication Guide or otherwise patient information sheet available to patients in the pharmacy that's more user friendly and useful for the patients.

We look forward to work with FDA on many of these topics as we move forward.

In conclusion, we'd like to thank you for the opportunity to participate in today's meeting. Again, let me express APhA's support for the PDUFA program and its ability

to support FDA's mission to promote and protect public health.

I will close be reiterating our recommendations that FDA continue:

Outreach to stakeholders;

Ensure opportunities for pharmacists involvement in post-market surveillance activities and pharmacogenomics;

Continue with the Drug Naming Review program and the review of DTC advertising;

Continue with an emphasis on education about personalized medicine activities;

Improve the REMS development and approval process by ensuring that a standardized system-based approach is utilized, that it involves input from providers in the development process and recognizes the clinical role that pharmacists can play in addressing medication use/misuse, and;

Finally, we look forward to working with you as we develop a new and improved Medication Guide or patient information sheet.

We look forward to working with the agency, consumers, other health care professionals, manufacturers and other stakeholders on these important issues.

Thank you.

(Applause.)

FACILITATOR TOIGO: Thank you, Marcie.

And Kasey will be our second presentation from pharmacists.

MR. THOMPSON: Good afternoon. My name is Kasey Thompson. I am the Vice President of the Office of Policy Planning and Communications at the American Society of Health-System Pharmacists. ASHP is a 35,000 member national professional association representing pharmacists who practice in hospitals, in organized health care setting including ambulatory clinics, hospital

outpatient pharmacies, home care and long term care.

I appreciate the opportunity to present the view of ASHP on the Prescription Drug User Fee Act.

FDA's public health mission is to ensure the safety and effectiveness of drugs and biologics and medical devices. No other agency or private sector entity serves this vital public health service. ASHP firmly believes that the allocation of sufficient federal resources to the FDA to meet its public health mission is a necessity, and that funding for the FDA should be achieved primarily through federal appropriations. The Society strongly supports increased appropriations for the agency and is working to achieve this through the work of the Alliance of a Stronger FDA. While user fees do not replace appropriations, ASHP recognizes that. With the agency's ever increasing work flow user fees are necessary.

My comments today will focus on how user fees should be used to improved patient safety.

I will discuss risk evaluation and mitigation strategies or REMS.

ASHP supports the current system of drug distribution which prescribers and pharmacists exercise their professional responsibilities on behalf of patients. However, society acknowledges that there may be limited circumstances in which constraints on the traditional drug distribution system may be appropriate, such as through a REMS.

REMS are the result of an evolution of risk management at the agency. Prior to REMS there were risk management and action plans or risk maps that were developed during the drug approval process for drugs that require additional risk management strategies. The Food and Drug Administration Amendments Act, which I'll refer from this point as "the Act," broaden FDA's authority by allowing

greater enforcement mechanisms and the implementation of REMS after a drug has gone to market. With this expanded authority, FDA should ensure the agency's risk management programs now in the form of REMS have one single goal, and that is patient safety.

With the Act, FDA was granted the authority to require REMS for certain drugs in order to help ensure that benefits outweigh risks. ASHP supported this provision and applauds the agency's efforts in implementing its enhanced authority regarding post-marketing safety of drugs. However, there are increasing number of drug products that are being assigned REMS, and there are cases where REMS may not be achieving the patient safety goals.

As REMS were developed and implemented, ASHP encourages the FDA to consult with practicing pharmacists are required under the Act. As the agency developed its recommendations for PDUFA V,

ASHP urges the FDA to consider requirements that sponsors and demonstrate meaningful input by practicing pharmacists from all settings in the design of REMS and conduct an analysis of the impact, including burden, on the health care delivery system.

The Act begins to address the issue of burden. However, we urge the agency to do more to minimize the burden on the health care delivery system to conform with REMS elements to assure safe use for drugs with other similar serious and to be designed by compatible with established distribution procurement and distribution systems for drugs.

The experience of our members indicates a pressing need for standardization and uniformity of REMS to help decrease the burden and interruption on patient care and pharmacy work flow.

The Society further encourages FDA to ensure the minimal strategy for REMS

assessment is completed for each REMS, as required under the Act, which includes an assessment with 18 months, 3 years, 7 years unless eliminated after the three period.

FDA should ensure REMS requirements preserve the pharmacist/patient relationship and also perform research on the impacts of REMS on patient safety, cost effectiveness and pharmacy work flow.

Our members' experience indicate that significant burden is developing with an increase in the number of products that require REMS. This will only continue to grow as follow-on biologics and other high risk products are introduced to the market and the agency's work load increases.

Additionally, since Medication Guides can be part of a REMS, the agency should consider the most effective way to provide written information to the patient. ASHP does not believe that Medication Guides are currently as they are currently produced

and used is an effective way to communicate vital safety information to patients. ASHP stands ready to work with the agency to develop new and better approaches to addressing patient medication information.

Our members have serious concerns that risk management tools are sometimes used for marketing promotion and economic purposes. ASHP believes that REMS should be used only for patient safety reasons. When developing a REMS, FDA should assure:

There is no lack of access to medication histories and no delay in obtaining medications;

No significant increases in provider work load, no variability in processes for hospital pharmacy staff and other staff, and;

No conflicts between hospital regulatory and accreditation requirements, insurance and patient demands

For example, no REMS requirement

should directly or indirectly create a situation where a patient has to obtain an injectable product from a specialty supplier and then bring that product with them for administration during an inpatient stay in the hospital; a situation that is sometimes referred to as "brown bagging," and one that circumvents vital safeguards in the medication use system.

Now let me talk about the Sentinel Initiative. In the post-approval phase the Agency Adverse Event Reporting System and Sentinel Initiative are an important element in the national electronic drug monitoring system. ASHP has participated in public workshops and has submitted comments in this important patient safety activity, and looks forward to providing as it continues to evolve.

The issue of drug shortages and recalls are the one that I would most like to talk about. FDA's policy is to prevent or

alleviate shortages of medically necessary products. In that, FDA should consider in its definition of medically necessary the impact of medication use factors.

If an unfamiliar drug product is introduced into a clinical setting, there is an increased risk to a patient's safety. The ASHP's worked with the FDA through the Society's Drug Shortages Resource Center to help notify the entire health care community of current or upcoming shortages, to help resolve shortages and to develop safe and effective alternatives to address drug shortages. However, as beneficial as these efforts have been, patient harm still occurs due to factors associated with drug product shortages and more needs to be done to address through PDUFA.

I would now like to touch briefly on the drug recall system. ASHP believes that the FDA must have authority to clearly communicate with stakeholders about recalls of

marketed products. A standardized recall notification should be used by manufacturers because it would enable practitioners and others in the drug supply chain to readily identify and respond to a recall.

ASHP recommends that the FDA develop a standard recall notification to be used by all manufacturers. Such notifications should:

Come from a single source;

Clearly identify the recalled product;

Explain why the product is being recalled;

Provide a way to report possession of the recalled product, and;

Give instructions on the disposition of a recalled product.

Additionally, FDA should be granted the authority to order mandatory recalls of medications in order to avoid the miscommunication that has occurred in past

voluntary recalls. FDA should also consider post-marketing reporting of adverse events and product quality issues to enhance the recall system.

Finally, ASHP supports legislation and regulations that promote greater patient access to less expensive generic drug products. Through the years the Society has worked to ensure generics are brought to market more safely and more quickly. ASHP encourages the FDA to consider requiring user fees for generic drugs.

The issues that I have just spoken about are the issues that ASHP believes to be FDA's primary focus for PDUFA V. Our written comments will elaborate on these, and other issues we intend to bring to the agency's attention. Moreover, we look forward to holding discussions with the agency as part of an ongoing stakeholder input as the agency develops its recommendations to Congress.

On behalf of the 35,000 members of

the American Society of Health System Pharmacists I appreciate the opportunity to present our comments to you.

(Applause.)

FACILITATOR TOIGO: Thank you, Kasey.

And now we'll hear from Barry Dickinson from AMA. After I get him technically ready.

DR. DICKINSON: Well, I didn't read the fine print. I thought you had to have slides to present at the meeting.

I also feel kind of compelled to issue a disclaimer of sorts. This morning we heard about comparative effectiveness research, off-label uses, patient medication information behind the counter class of drugs, advisory committee structure and function. I'm not going to be talking about any of these, but that doesn't mean we're not interested in them. So these are clearly, particularly the off-label use and the

comparative effectiveness research are weighty, legal and regulatory issues. I'm not quite sure how directly they relate to the user fee issue, but nevertheless they're important issues and we certainly have our own views on those.

Just to note, the AMA is an umbrella organization. We have more than 110 medical specialties in our House of Delegates, 50 medical state societies along for good measure and several other professional interest medical groups. So when you're talking about risk communication or REMS, or risk management, you know the relative interest is going to be product-specific and specialty-specific. So, not many people other than dermatologists care much about Accutane. The same thing could be said for clozapine and psychiatrists and down the line.

On the other hand this kind of umbrella structure can provide an appealing kind of benefit because we have an existing

communication infrastructure in place where we can reach out simultaneously to all of these different physician groups and state medical societies if there was, for example, a specific message that needed to be communicated that was clinically relevant and, for example, related to a particular safety issue.

You can look at our policy database and we have policy statements going back to 1978 in which we express strong support for adequate funding for the FDA. You know, 15 years or so before PDUFA was invented.

We have publicly supported previous cycles of PDUFA I through IV on the assumption, for the most part, that the primary purpose of user fees is to make the drug approval process as efficient as possible, And as you notice on the slide, without compromising standards for improved efficacy and safety. So we all know that there are critics who will make the point that

the larger the percentage of your budget that comes from the industry to regulators, there's perhaps some tipping point at which there's inherent conflict of interest that starts to become a concern. So, I'm not here to make a statement one way or another on that. We support adequate funding for the FDA, but I think everyone needs to be cognizant that at some point you have to have, perhaps, mechanisms in place to be able to respond to those kind of concerns so that it makes your path easier as you develop whatever PDUFA V is going to look like.

So here's the first question: What is your assessment of the overall performance of PDUFA IV programs?

I had difficulty answering this question. You know, as outlined in the Federal Register notice for this meeting, the agency by its own admission says that we had to devote a lot of our resources to the new statutory authorities with passage of FDAAA

with titles IV, V and IX.

I wasn't able to locate a annual performance report for the PDUFA goals for drug review times, so I'm not quite sure what the current situation is, although I think some of the slides that were part of the webinar material before the meeting here, seemed to indicate that there's maybe been a little bit of backsliding in terms of we have more applications now that might not have met that review deadline point.

So I guess as the next couple of years of PDUFA IV falls hopefully by the time we get to see some actual publicly available performance on those measures. Just kind of have to wait and see.

Again, we got the five year plain for enhancing the FDA drug safety system, which many people have alluded to. But I guess the annual assessment of that is not quite ready or hasn't been forthcoming.

So, I'm pretty much going to take a

pass on answering the first question and focus on, as we move forward, what's good, what's bad. Well, we'll discuss what's ugly.

The first slide here notes current AMA policies that are strongly aligned with the performance goals of PDUFA. So the first two points here actually just cut and paste it out of some of our policy statements.

The AMA supports implementation of improved post-marking surveillance process and risk communication process.

Broader use of target and post-approval of studies.

And institution of Active.

And Sentinel events surveillance and Active data mining to identify safety signals for appropriate action and follow-up.

So overall then we would say that the AMA enhances some modernization of the drug safety system, assessment of current and new methodologies to maximize the usefulness of tools used for collecting, adverse event

information throughout the life cycle, developing and validating risk management and risk communication tools including mechanisms for physician and patient communication about both the benefits and the risks of drugs and biologic products. And then as the FDA well knows, the IT infrastructure to be able to handle that stuff and to link appropriate other data systems as part of the process of mixing maximal availability and usefulness of those signals.

So, we're all aware that Congress substantially increased fee funding for drug safety in PDUFA IV. So, my third comment there in a different color means it's more important, is that this is our hope for the future that the FDA must make substantial and continued progress in implementing systems to detect safety signals. Then I think at that point I think the FDA would agree that they believe that they are well positioned to deal with that signal, how to determine if it's

real, what needs to be done to determine of it's real. And then the third piece of the puzzle is when you get that emerging safety information, how do you communicate it to the clinician and the public so that they know what to do it, that it becomes clinically meaningful? That there's not unintended harms that may be associated with that message that would, for example, led patients to stop regular medication which maybe they shouldn't. And that discontinuation could be associated with adverse events in their own right.

So there's a lot of stuff going on. I understand that and appreciate it.

The physician side out there, the clinical practice environment, doesn't really have a sense right now that there's been a lot of movement and improvement that affects their daily lives. But I'm hopeful that the various initiatives and best practices and so forth, and workshops that are underway will come to fruition. And a few years from now we'll be

able to say that we've made some real progress.

And then the second piece in terms of our current policies is that we support pre-review approval of DTC. That's a subject that came up quite a bit this morning from a consumer and patient perspective.

So I'm going to stay at the 30,000 foot level and just identify three areas as we move forward. They're currently part of the PDUFA goals that should be emphasized.

And Marcie mentioned in her presentation personalize medicine. So we're all familiar with the fact that a number of genomic-based applications have advanced that are personalizing the delivery of care by enabling risk prediction, therapy, prognoses that is tailored to individual patient. So we support strategies -- there's a couple of current strategies in PDUFA IV that speak to this issue.

One is development of a guidance

for enriched clinical trial designs. And then collaboration with other groups on moving forward with the whole biomarker question as an end point. And so we support that, and anything else that would speed up the process and get drugs to market for what was mentioned this morning in patient panel, for safe and effective use for that individual patient under certain conditions, for certain diseases and under certain circumstances: The whole concept behind tailoring individual therapy.

And then I would just note that on the physician's side substantial challenges remain. There's not a good comfort level with genetics and molecular medicine amongst today's practicing physicians.

There is certainly, by in large, a slow generation of validity and clinical utility of many of these genetic tests. And I would just note that we worked previously with the agency a few years ago to develop course for pharmacogenomics. Something about 1300

physicians took that course. And we're certainly willing to work with the agency on further initiative on pharmacogenomics, personalized medicine. And that goes for the pharmacy groups as well since it's an area that also is of some interest to practicing pharmacists.

A second area, a second comment is under the whole concept of validating risk management and risk communication tools. So about three years we convened two meetings between the staff and the agency and physicians to discuss the targeting of drug safety information for specific physician audiences. This is still at a point when the whole RiskMap Initiative and guidance was underway before the invention of REMS with FDAAA.

And we did this because medical specialty societies are considered to be the most credible source of clinical information by its physician members. Physician members

of the American College of Cardiology is going to pay a lot more attention doing something they get from the College than they get from us, or probably from the FDA or anybody else. So it's a treasured line of communication that already exists.

And so what emerged from these discussions was what we call euphemistically a network of nodes. And under this concept individual medical specialty societies would designate a subcommittee, a person, a staff individual to be a liaison, or a node, to the FDA and similarly the FDA would identify physicians or other staff within the agency as liaisons or nodes to the individual medical specialty society. This identified network then would create a sustained and ongoing relationship, and therefore conceptually allow for better communication between the societies and the FDA.

This could be a two-way process, of course, also. If there's emerging information

that specialty became aware of, they could communicate back to their node within the agency to address whatever needed to be addressed in that fashion.

So we ended up, we did establish, we got our liaisons from our medically specialties. But we never were able to get the project farther along as other things came up that demanded attention, as we've all heard about. And so we're just here under the rubric of risk communication PDUFA IV to ask the agency examine reinvigorating this concept and devoting staff resources to its implementation.

And then finally, for this panel so far a common theme has been the REMS. And so I'd like to congratulate the agency for doing what collaborative practice acts and disease management programs have failed to do, which is unite physicians and pharmacists under the same banner. So we all have concerns about how the REMS program has played us. They've

developed at a brisk pace, including the deeming of previous risk drugs that had RiskMaps. I'd just like to point out that under PDUFA IV's five year drug safety plan, the FDA noted that user fees would be used to hire additional risk management experts to be engaged with reviewing proposed and implemented RiskMaps and its successor REMS.

And I'd like to take a step back here and go back to the guidance that the agency developed for the industry when the RiskMaps were evolving and they established a RiskMap tool kit. And the agency in their guidance advised the industry to "maintain the widest access while minimizing burdens and to identify and seek input from key stakeholders." And so all we're asking the agency to do now at this point in the world of REMS is to follow their own advice. And so like the pharmacy comments that we heard previously were suggesting that the REMS process must be more transparent, that the FDA

should establish and organize the systematic process for gathering input from the physician community and other stakeholders on specific REMS proposals early in the drug review process.

There's also comment this morning from a patient panel, I think, about the need to examine how the various safety initiatives that have been rolled out including REMS are affecting patient access or are they affecting patient access. And I don't know that you actually need a GAO report. I believe that the statute of FDAAA as it was written says right in it that REMS cannot be unduly burdensome on patient access to the drug, or on patients who have difficulty assessing health care. That to me means there should be some ongoing evaluation process to see if this happening as more and more REMS with restricted distribution features, in particular or elements to assure safe those; as those proliferate it seems to me that we need to

have some reassurance that we're not getting into a situation where these programs as they develop are in fact being unduly burdensome on patient access or on patients particularly who are in under served areas.

And so that's my final comment. And thank you for your attention.

(Applause.)

FACILITATOR TOIGO: Thank you Barry.

And just on the network of nodes since I think the name has morphed, but we are working on it. Probably just not as fast as you would like us to.

And now Mark Del Monte will talk to us about the perspective from the American Academy of Pediatrics.

MR. DEL MONTE: Thank you, Terry. And thanks for inviting the Academy of Pediatrics to come and be a part of this meeting. I think it's very, very important for the perspective of children to be at the

table. And I know a number of groups this morning have addressed pediatric issues, but I'm going to focus on those specifically.

My name is Mark Del Monte. I'm the Director of the Department of Federal Affairs for the Academy of Pediatrics.

AP is an 80 year old medical association. We were founded by a group of pediatricians to promote the health and well being of children and maximizing the life success of every child.

We have 62,000 pediatrician members across the country and increasingly internationally. And from primary care pediatricians to academic subspecialists across the board the pediatrics.

PDUFA has been very important to us, and we have been a participant in PDUFA reauthorizations each time. And I'd like to associate us with a number of the comments that Barry made for the American Medical Association, particularly on pharmacogenomics

and the need to communicate in physician-home societies. I those are really important essential elements, particularly in pediatrics as well as the comments about REMS.

In the last go around for PDUFA IV, it seemed like only yesterday that we were talking about PDUFA IV. I guess it's time to start talking about PDUFA V now. The Academy participated with a number of groups, advocacy organizations called the Alliance for Drug Safety and Access, or ADSA.

Diane Dorman, whom I believe you heard from this morning was a key leader in that coalition. And I'm looking forward to forming up again as PDUFA V gets rolling to continue to work in coalition with those groups.

PDUFA has to strike the right balance between speeding drugs to market and patient access and patient safety. And this principle is no more important for pediatrics then for everyone else. The balance of access

and safety is critically important in pediatrics where off-label use is the necessary standard of care. So in an environment of off-label use, the maximum amount of information is necessary to be communicated to providers and patients, even when that information is not ideal for what you would want to have in particularly labeled indications.

So as a result, children over the history Food and Drug regulations have sort of been the canaries in the mine shaft, the early warning system for problems of drugs and devices. Some have called them the ultimate orphan population. Diane Dorman from NORD says that it's okay for me to say that. So I will repeat that: Children are a vulnerable population.

They're also a variable population. Children are not a monolithic group. So a neonate is very different from a toddler, is very different from a young child, from a

young adult, an adolescent, across the life span. So they're both vulnerable and variable. That creates enormous challenges in drug development.

Many of the significant milestones historically in U.S. drug regulation have come as a result of harmed children. So it's a well known example for sulfanilamide in 1937 led to pre-market safety requirements of the Food Drug and Cosmetic Act. And then thalidomide in the 1960s led to pre-market efficacy requirements.

So you can see the innovations of regulatory approaches that happened largely as a result of incidents involving children.

The irony often has been, however, that although those regulatory innovations have occurred because of children, the benefit of those regulations has inured mostly to adults. So off-label use continues to be the standard of care in kids.

Despite the work that we've done

over the last 30 years, the vast majority of drugs that are used in children are not studied in children.

Since 1977 AAP has advocated strongly that all medicines be tested in kids that are used in all pediatrics populations. In fact, in 1977 was when AAP first said that not only is not unethical to study drugs in children, it is unethical not to study drugs in children which was a see change in the understanding of clinical trials practice for pediatrics at that time.

It was a first step forward in the history of PDUFA when it was first authorized in 1997, there was a pediatric exclusivity provision, which was the first there was an incentive to study drugs in children which began the long road that we've been on and changed the practice as we know it. That incentive was reauthorized in 2002 as the Best Pharmaceuticals for Children Act, and the Pediatric Research Equity Act followed along

behind it in 2003 after the Pediatric Rule was struck down by the courts. In PDUFA IV BPCA and PREA were reauthorized along with the rest of the legislation that made up FDAAA.

The Best Pharmaceuticals for Children Act, just to orient folks about where we are, BPCA offers new or existing on patent drugs an additional six months of market exclusivity for conducting FDA requests that are made through a written request. Applications or supplements with new pediatric labeling as a result of BPCA studies fall under PDUFA's priority review timelines. That's a key element of the success of BPCA, and we will advocate to continue that.

In the recently passed health care reform legislation, the Patient Protection Affordable Care Act extended BPCA's exclusivity incentive to biological products as well. And so we look forward to working with CBER in the implementation of that provision.

The Pediatric Research Equity Act is the requirement that all new drugs conduct pediatric assessments. That requirement is triggered by coming in with a labeling supplement or other supplement. And PPACA, is that the agreed upon pronouncement of that acronym, requires that preassessments also follow for non-interchangeable follow on biologics. So the two provisions that went with PDUFA last time have now been extended into biologics. And we're hopeful that we can continue that.

These two laws do have a track record of success. And it's interesting because it wasn't entirely clear when pediatric studies were induced by BPCA or required by PREA what exactly the result was going to be. And I think Diane Murphy from the Office of Pediatric Therapeutics at FDA says this best when she says that we learned that we didn't know what we didn't know.

So pediatric populations are in

fact more variable than we thought in the beginning, and we learned increasing variability. Young kids clear some drugs faster than older kids; I mean the results have been much different than anything you would have expected which only serves to highlight the need for increased pediatric studies in children.

BPCA and PREA studies have revealed safety issues. They have altered dosing both upwards and downwards so that sometimes younger populations get more per kilo dose than older populations, and the reverse is also true. And some drugs that were the standard of care were shown to lack efficacy at all and were abandoned, and one less drug that kids have to take.

So the point here is that the studies in pediatrics actually reveal information across board that was not previously known or expected.

To date, as of February 24th, 335

medicines have been relabeled for children as the result of BPCA and PREA. I think it's fair to say and the American Academy of Pediatrics thinks it's fair to say that BPCA and PREA have changed pediatric practice for the better for kids.

So, dispute that record of success as PDUFA V comes forward and the reauthorization of PDUFA and other drugs bills associated with PDUFA come forward, I think we need to say that we've had a good run but much more is needed. Much more studies need to be done to understand the complexity of kids and to solve some of the intractable problems that we have in pediatrics to speed drugs to market and increase the understanding of their safety.

Off-label use, despite the 335 drugs being relabeled, still remains the standard of care for pediatric populations, in particular neonates where those tiny babies are receiving lots of medicines, most of which

are off-labeled. And we need to do something about better understanding of therapeutics in that population.

Other issues that we need to address going forward is that the adult requirements, the Food, Drug and Cosmetic Act does not expire, but the BPCA and PREA both do and we need to look at whether or not the renewal requirement on those laws is appropriate. We certainly believe that safety and efficacy protections for children should not expire.

Right now since PDUFA IV there's been a greater coordination between FDA and the European counterparts in the EMEA to share information and avoid duplicative studies. This is a very promising set of activities so that children are not studied twice for the same indication or children on both sides of the Atlantic are not going through the same clinical trials with the same results. So thinking about how to better coordinate with

our European counterparts is a real opportunity here to minimize the effort and maximize the results.

The other thing that the Europeans are doing is requiring thinking about pediatric populations much earlier in the drug development process. In fact, in the EMEA legislation the pediatric plan, the pediatric investigation plan or PIP as it's known there, the PIP has to be submitted very early even after Phase 1. We could talk about the right moment on that, but the earlier we think about kids, the better. And so I think we need to think about how to integrate that kind of notion into our drug regulation process so that kids can be thought of earlier.

And as I mentioned before, the implementation of the new pediatric provisions in the health care law and how to move the kind of incentives and requirements that have been so successful in drugs into the arena of biologics.

Let me stop there and with a couple of things.

First, let me thank James Baumgartner from AAP for his assistance with the slides. And then also thank the extraordinary health professionals at FDA. There are a number of folks within the Center for Drug Evaluation and Research, within the Office of the Commissioner, within the Center for Biologics and all across FDA that really are champions for children and have made the implementation of PDUFA V and the other laws a success for children.

In particular, I'd like to thank Lisa Mathis and her team at CDER and Diane Murphy and her team in the Office of Pediatric therapeutics who have really been champions for kids right along. And we look forward to working with them and FDA in the next steps of these processes.

(Applause.)

FACILITATOR TOIGO: Thank you,

Mark.

Any questions from our listening panel for our health professionals? Okay.

Then we very much appreciate your participation and we look forward to working with you over the next nine months or so. Thank you.

Could we have our three panel members for Panel 5. The Scientific and Academic Expert Perspectives.

Okay. First we're going to hear from Christopher Milne, he's the Associate Director, Tufts Center for the Study of Drug Development.

DR. MILNE: Thank you, Theresa. And thanks for FDA to inviting me and to all the participants here.

I know I didn't have to bring slides, but we are the big picture guys so I brought pictures. And I could have done what we did in the summer, which was kind of interesting, but I thought you'd rather have

something about drug development.

So that's what I'm going to talk about. It's kind of I am mindful of the two questions of the two questions that we were asked to addressed, so I'm going to sort of present a PDUFA sandwich, if you will. I'm going to talk a little bit about what I think PDUFA has produced in its three or four iterations. And then talk about, I think, the challenges we have to think about going forward as a way of leading into what I think we have to address in PDUFA V.

That being the case, I also hope that I don't commit the DTC error that my words are not reflected by my pictures. I think that that's, hopefully, not a problem since they are my slides.

Anyway, so first slide is dealing with, you know we can -- my pointer has kind of gotten weak.

All right. Well if you have really good vision, you can see my little red dot.

But I think that's just more annoying than anything.

You can see where PDUFA was enacted and you can see that the approval times did in fact go down from three years to a little bit over one, one and a half years on average if you average those time periods out. And that was part of the purpose. And as you heard from, I think, some of the patient advocates and other people, getting the products to market is important. It's not the sole focus, obvious, of the approval process but it certainly does help to get it to patients more quickly.

However, on the clinical side, in other words what happens once you get your IND in and then you're getting ready and doing all the studies you have to do over a six or eight year period in order to put that approval package together, obviously it was a little bit different in terms of the impact. You can't lay this all at the feet of PDUFA or

FDA, or anyone in particular. As I'm going to show you, there were tremendous complexities and challenges that were somewhat anticipated and somewhat -- oh, thank you very much.

A friend in need is a friend indeed. Remind me to give you that 10 bucks I promised you later.

FACILITATOR TOIGO: For that I might have found one.

DR. MILNE: Sure. More funding by that.

So you can see that it was clearly going up in terms of the clinical pot. And PDUFA was enacted, and it sort of went up and down. And there has been an overall impact where it is somewhat shorter in the overall time, obviously because the approval time has been going down. So you've knocked off a year and a half there. But, again, in terms of clinical time we still have some work to do. And you'll see especially this is in regard to the biopharmaceuticals.

So that last slides we're dealing with the new products that were approved by FDA, particularly CDER over a period of time so that included both new chemical entities as well as the biologic side, the new significant biologics.

This is just looking at monoclonal antibodies and recombinant proteins so the new biologics, where, of course, a lot of people say the new needed products are coming from, where the innovation is coming from. They're about 25 percent now of what's on the market and expected to be much greater. So, obviously, a focus of the concern for us. And you can see that that time period is growing.

Yes, again we've had some impact from PDUFA in terms of lessening the approval time, but you can see that clinical time is just continuing to grow; the amount of time it takes to kind of put those packages together. So this is obviously a concern, something that we have to think about in terms of what can be

addressed in PDUFA V.

Another thing, of course, the big problem is the clinical success rates sometimes called the attrition rate if you're sort of the half glass, the glass is half full, half empty type of person. But we like to refer to it as the success rate, which has dropped to 16 percent. It was formerly in our previous studies about 20 percent. Some other studies that people have looked at, CMR in looking at more of a European mix, said it's down at 11 percent. In any case it's not good, when you think about only one out of ten drugs are getting approved, maybe one out of eight drugs. That's certainly a concern.

And the other thing that you have to think about, though, is you have a lot more to learn if you think about it from the failures then from the successes. So we talked a little about it, I think in some of the previous speakers, about getting some of that -- some way to have everyone benefit from that

failure information. So we can only think you're going to say, well what's not working? That's something that hasn't been done so far very well. I think the Critical Path Initiative had some ideas that they would be able to do that saying that FDA would be the only one that could really put that information together and use it. That hasn't happened. We'll talk a little bit about Critical Path at the end.

But as you can see, it depends, of course, on therapeutic area so we're not only dealing with a whole set of complexities and factors, but then you have to sort of titrate that by the therapeutic that you're in, and the therapeutic area that you're working in. And, of course, that's really a concern when you get down here to CNS drugs when we heard about the antidepression problems and getting good products there with a clinical success rate even under 10 percent, or a success rate overall of under 10 percent.

Oncology is getting a little bit better. We see a tremendous amount of effort that's going into oncology. That's great. But obviously there are some needs down here too.

Anti-infectives. Again, you're getting kind of an AIDS boost there because a lot of the anti-infectives deal with the antivirals that come through the AIDS programs. But there are also problems there in terms of challenges for new antibiotics that we have to be thinking about going forward.

So, again, this is the part where we're thinking about, what do we have to address in PDUFA V? What have we heard a lot about? The needs of patient access, showing patient access, streamlining the process. And again, here we are looking at those three big areas: Anti-infectives, central nervous system neuro drugs, oncology. You can see that those really command our attention in terms of where the work is taking place.

Almost -- more than half of all the work taking place in development is happening there.

And it's not surprising that in order to address that problem there's a lot going on in the industry. And I think that has to reflect it and complement it, if you will, with some actions on the part of the agencies, FDA in particular.

You can see in cancer and infectious and neuro there's a lot of partnering going on. So we're trying to marshal the resources out in the industry to deal with the complexities, to make things happen. And when you compare those with the other areas, I mean they basically dwarf them, especially cancer. And this is the average for the other 12 therapeutic areas, 12. So I mean it's almost ten times as great, if you will, how much partnering is going on, how much they're trying to, again, work with each other, the different academic groups and

companies, and private/public partnerships to deal with the tremendous scientific complexities.

And also the other thing that's a problem -- not a problem. It's part of that challenge is that there's a lot of new players involved. And that also presents challenges for FDA in dealing with these new companies who are doing late stage R&D. And what this is showing you is that 60 percent of the oncology products are owned, if you will, in late stage trials by the top 20 companies. But there's quite a few, and it's growing, that are not. And the same thing here with CNS, you can see it's even greater, the contribution of smaller companies.

Those are late stage trials. That means they're probably going to take those all the way. They're going to try to take them and get the application package approved, maybe it's going to be their first one that they're going to go through that whole process of the

agency, a lot of challenges not only for the industry itself, but for FDA itself. Something, I think, we have to be looking forward to in PDUFA V.

Another thing, it's just getting more complex. We have to think about that complexity in asking for more and more processes and tests and studies that need to be done. And what's that adding to the challenge of getting this product on the market and the patient access that was referred to by several of our speakers?

You can see this was a study we did on just basically looking at protocols, your basic tool for what you're going to do and how you're going to do it. And how that has increased -- and, again, this is pretty recent work -- how that has increased in complexity over the last few years.

Now risk management. I don't want to get into this. A lot of people have mentioned this. It's obviously a growing area

that companies have to be focused on. It's also a growing area that FDA has to be focused on. We're all mindful of the fact that this is increasing the workload for FDA as well. But you can see what it used to be in the good old days when there was just risk management plans. And now, you know, we've kind of graduated, you kind of build under this management plans and now you're dealing with REMS. Again, you already have your risk management plan even in place, maybe now you have to build a REMS plan on top of that and an implementation, do the reassessments. And so there's, again, a whole other increase not only in quantity, the quality of what needs to be done.

And then you have that globalization factor. Things are moving outside the U.S. You can't just focus on what's happening in the U.S. It's a global enterprise. This is just the increase over time in FDA regulated clinical trials

conducted outside the U.S. And you can see even the proportion that's done in Western Europe where, obviously, they have a fair amount of similarity in terms of the oversight that takes place. Even that's lessening in terms of where they're happening in different places of the world where, yes, there's GCP and often there's some ICH involved. But there's still a lot more concern in terms of FDA dealing with that data. And this is just from FDA regulated clinical trials. There's still the whole other aspect of trials that are done, not under the auspices of an FDA IND, but are just submitting data, parts of a data application package. A lot more work for FDA. A lot more concern for all of us, again, moving forward to make sure that data is good quality.

Although we have done a couple of studies, and I've seen some others, which don't indicate that just without looking at the situation further, that automatically have

to be concerned about trials that are done overseas in terms of the data quality. Sometimes they have certain aspects that actually have come out better so far in terms of what they're doing and how they're doing it. Because often, when you think about it, being a clinical investigator in some countries overseas is actually a better job than it is here. So they have highly skilled people doing jobs that we might have being done by lesser skilled people here.

So, again, something that has to be done carefully. A lot of work for all of us, but especially FDA.

Here's the big thing. We talked about, finally, I think, in the afternoon about personalized medicine. Well, there's tremendous scientific challenges. We're in the process of doing both an interview and a survey project with companies. Tremendous scientific challenges, practical challenges. I mean, there's something like 1600 genetic

tests that have to be integrated into making sure that we understand how to use them, how they should be used. Talk about the educational process that has to take place with the physicians. But they do say that one of the challenges also is the regulatory challenge of getting FDA to understand what's needed and to make sure they have the science base to deal with it. FDA has talked about it itself, the regulatory science needs that they have.

You got adult vaccines, another area again stretching out from child vaccines into areas where now adults are more likely to be vaccinated. And what that means in terms of health care costs as well as, again, problems with vaccines, of course, is you are dealing with basically healthy people. So now you are applying therapeutics, in this case preventatives, to healthy people increases that -- changes that benefit risk balance that you're looking at.

Biomarkers we know are what's going to drive personalized medicine forward. A lot of work to be done there.

Again, these are expanding. This is the cumulative growth rate that we're looking at in these areas over fairly -- these are not terribly distant futures that we're looking at, from 2012 or so to 2020. This is where the industry is really focusing its attention. A lot of this is coming down the pike real soon, and FDA has to get ready for it. We all have to prepare, I think in PDUFA V, to think about it big time.

Nanomedicine becoming a reality, not so much just a book by Michael Crichton anymore. It's definitely a concrete reality.

Again, this is just some of the newer techniques that are being used. Electronic data capture. We all have to deal with the electronic nature of what's being done.

Something that I think people don't

realize about the Health Care Reform Act, let's call it Obamacare because that's more of a fun name, is the tremendous impact in medical information technology. Again, the Sentinel Program is another one and now that's going to be used and the tremendous needs in that area that are going to be something we're all going to have to deal with very shortly.

So I know my time is getting short, but I just want to say that, you know, it's not as if the FDA wasn't already busy. I mean, here we deal with, just taking a quick look a couple of years ago the numbers of contacts they had with the public in a number of different ways. And I had to use exponential graph paper in order to show it because, again, we're talking like 3 million, and 30,000. And, again, so there's a lot that's going on already. They definitely have to prioritize things. I think they really need the help from industry to deal with this. I think some of these conflict of interest

issues that are coming up, as well as there are provisions in the Obamacare act that deal with conflict of interest. I think we have to think very carefully about how to make sure that those are not an impediment to getting the job done.

Because again, safety, efficacy, quality are only halfway of what you need to get a product to market. You can see that, of 2,000 drugs that Farmer projects followed from 2000 to 2008, about 40 or so percent were efficacy, safety and quality. Maybe the other ten percent were quality issues or just practical issues. But 44 percent were discontinued for business reasons. And business reasons is, again, that covers a lot of ground. But definitely one of the things it covers is this, the figure that everybody loves to hate, the cost of drug development.

It used to be that it was a generally known figure of $800 million. Well, that's old. That's about ten years old. Now

we're talking about somewhere around $1.3 billion, somewhere between the cost of what it takes to get a biopharm on the market and what it costs to get a chemical drug or a regular pharmaceutical on the market.

And, again, this takes into a lot of issues in terms of -- it accounts for failures. Only half of this is out-of-pocket cost. It counts the time, cost of money, the opportunity cost.

You take something ten years you've spent $100 million. That $100 million is worth a lot more ten years later. But still, it's a significant barrier that we all have to face.

And again, and part of it is the greater complexity, the lower success rates. These are issues that we can address.

We did a modeling where we showed that if you could just raise the success rate by a few percent, you could knock off anywhere from a quarter to an eighth -- from an eighth

to a quarter of this tremendous burden from the totality of what it costs to bring a drug to market.

That doesn't seem like an unreasonable target or goal to have. I think those are the kinds of things that we should be thinking about that we can do that are very doable.

So anyway, from my PDUFA -- maybe you call it a wish list. I'm not even going to say the FDA should do all this. I just want to say these are talking points that I think we should think about.

Again, remember FDAMA gave us that wonderful mission that FDA should help promote health care products as well as protect the public. Obviously, their public health mission. So let's not forget about that promotion side of the mission.

And again, you know, benefits and risks. The AMA said oh we can't even say risks and benefits. We must say benefits and

risks. I think that's a good approach that we have to make sure that we're not -- on the one hand, industry, on the other hand can't forget that they have to be attuned to the risk side as well as the benefit side and FDA should do the reverse.

So let's simplify, not amplify the regulatory scheme. We actually heard some of this. I think what you need, maybe GAO should do it, maybe not, in terms of, let's look at some of the new requirements and let's see, are they cost beneficial? Do they do what we think they should do? And if not, then let's simplify. There are certainly enough things that we have to do that are absolute that we can perhaps simplify some of the things that are not working out so well. This came up in a recent advisory committee meeting where they were talking about a new test that looked very promising to look at transfer mediators for drug-drug interactions. And then one of the committee members almost innocently said

"Well, gee, what are we going to take away? Because that seems like a really good thing to do but it's pretty expensive and there's already a lot to do and we're not really even sure that that works. So is there something else that we can take away maybe from this panoply of tests that companies have to do?" Well, I think it's a very good question that we have to think about going forward.

Equal medicines for all, you heard about. Pediatric exclusivity. Let's remember, that's working. Let's not sort of play with things, reinvent things that don't need to be tinkered with too much.

The priority review vouchers. That's something I think we could perhaps look at and see if there's a better way to increase attention to that, if you will. That's an incentive that was put in the last go-round for neglected diseases giving people who want to develop neglected diseases something that they can trade up, if you will, or use

basically to get some profit from this, again, somewhat expensive process of developing medicine for a patient population that's not going to be able to afford it itself.

And again, I talked about Critical Path Initiative. And you've heard a lot of people talk about how we need a lot of attention to some of the new adaptations that are out there for how we get clinical trials done if there's a problem with appropriating funds through Reagan-Udall to get CPI kicked off or to keep it functioning, then maybe there's a way we can spin off from the Innovative Medicines Initiative, which is working, or it seems to be working in terms of the way they have it set up at least, in Europe. And the mechanism for that could be under harmonization. We already look at joint scientific advice together. Maybe there's some other ways we can kind of use some of that to look at some of these sort of bump-ups that we need, revamping of the clinical trial process.

Also, maybe a way to address some of the issues with making sure that the new conflict of interest provisions do not put a chill in this nice, I think, useful relationship that we have between academia, the medical profession, patients and the industry that seems to have been pretty successful so far.

But some other things that I think ought to be talked about would be regulatory signs and translational medicine. Maybe it's not going to work for PDUFA funding, maybe at least it ought to be in there so that when the funding becomes available through the NIH Foundation or some other mechanism, at least those pieces will be in the picture as something that's needed going forward.

Thanks.

FACILITATOR TOIGO: Thank you. Dr. Milne.

And your pictures followed your words. And our consumers and our patients and

our health professionals stayed on time, so we built in this little extra time for the academics figuring that they might just go over a little bit.

DR. MILNE: Well, my reputation precedes me, yes.

FACILITATOR TOIGO: So Dr. Benner will talk to us next from Brookings.

DR. BENNER: Could I borrow the laser point? I'll pay the user fee.

Well, good afternoon, everybody, and thank you to the FDA for the invitation to be here at this important listening session.

Certainly the Engelberg Center for Health Care Reform at Brookings, which as all of you know is led by former FDA Commissioner Dr. Mark McClellan, is very active in a number of issues related to PDUFA. But I'll be talking a little more broadly about mechanisms by which we might improve the availability of safe and effective treatments today.

There are, as all of you know and

have heard already today, a number of important and strongly held views and opinions about PDUFA. And those are shared by stakeholders in predictable ways.

The first might be that PDUFA has shortened review times for most classes of drugs, and this has benefitted many patients who otherwise didn't have access to good alternatives. One estimate suggests that this has saved between 180,000 and 310,000 lives. But at the same time, there are also concerns.

One concern is that PDUFA's deadlines might have the potential to tax already thin and overburdened review teams. And some observers have raised concerns that this might cause reviews to be rushed or put through incompletely according to those deadlines.

And a related concern is that based on some research PDUFA may have led to a higher rate of post-market safety problems including things like black box warnings,

voluntary dosage and dosage for discontinuations and product withdrawals. Now this one in particular is uncertain, it seems, since studies don't agree on this as a fact, including the FDA's own analyses which didn't reach exactly this conclusion. But, suffice it to say, there's a range of strongly held opinions about PDUFA. And the real challenge is that the current methods available to FDA and to its regulated industry for the development approval and post-market evidence development activities is that it creates trade-offs between accelerating approvals on one hand based on more limited information in order to reach patients more quickly, thus improving access for patients who don't already have good alternatives and on the other hand spending more time and resources to reduce the uncertainty about the chance of harm from an unsafe product or a product that might be unsafe in a subset of the population.

Now, this balancing act probably

wouldn't be so difficult if we all agreed on the acceptable level of speed to market and the acceptable level of confidence around the risks and benefits of medical products. But the fact is that we don't. Opinions on these things both differ, as I said, sometimes in predictable ways depending on who you are, who you represent and what disease state we're talking about.

So it seems to us that the way forward involves finding a balance that requires new tools and methods that can improve speed and reduce uncertainty. That is, applying some weight here in the middle of the seesaw so that we don't have to balance these off against each quite so often.

So in particular, I'm going to focus my remarks today on two areas that illustrate the kinds of innovation that can both increase speed to market and decrease the uncertainty about product risks and benefits. The first is going to be post-market

surveillance and the second will be pre-market development science.

So talking first about pre-market development science. Certainly this is one area where we can make progress in faster availability of safe and effective therapies. And I just want to preface my remarks here by saying this has been an area of considerable collaborative work at Brookings with many people whom I see in the audience today.

We worked consistently with Ellen Sigal and the Friends of Cancer Research on these kinds of issues in cancer.

We've worked with FDA, with the Critical Path Institute, with many of the patient advocates I see here today, and with many of the industry partners I see here today.

Now these are keys, as we see it, to reducing the clinical time to market that Dr. Milne referred to, and also increasingly the predictability of product risks and

benefits.

So the first step, and I'm admittedly over-simplifying a very complex domain of pre-market research and development. But I'm just going to cover four areas today.

And the first is better translational research. This involves building on the explosion of OMIC data, as we now call it, so that we can do better disease modeling to understand the natural history of diseases for which we don't have good treatment alternatives today. Particularly relevant in areas like cancer and the neurodegenerative diseases. And then also validating biomarkers of treatment response so that we understand markets that not only predict the progress of a disease, but also any given patient's response to a treatment in that disease.

The second is the development of more reliable diagnostics, also a key to personalized medicine and better predicting how patients will respond to treatments. We

need reference standards and we also need accepted, efficient, independent sources of testing to demonstrate the clinical validity and utility of new diagnostics.

Third, we need to develop more efficient mechanisms for clinical trials. Again, very easy to see how more efficient trials that require fewer patients and less time can speed products to market. But also if they provide all of the pieces suggested here, can also help us better predict product risks and benefits.

So one area in which trials can become more efficient is if we agree on data submission standards. And this is one area where Brookings, along with ASCO, AACR and the FDA have done collaborative work. And I can refer folks to our website at the end of the talk for additional details on that. But there are publications forthcoming on questions like: How important is it to collect low grade adverse events in

supplemental indications for cancer therapies?

A second area for improving the efficiency of clinical trials is surrogate endpoints. How do we know whether the treatment works or not? Well, perhaps we don't need to follow treatments to the ultimate final clinical outcome. And in cancer this is illustrated by the question of whether we need to understand improvements in overall survival or whether there could be surrogates like progression free survival or even more upstream surrogates like biomarkers that could help us understand the effectiveness and risks of the treatment.

And then finally, adaptive designs. Certainly a promising statistical development which so far seems to be limited to use in Phase 1 and 2 trials, but there's certainly promising models and possibilities that could help us use adaptive and other efficient statistical designs for trials in later stages of development as well.

Fourth, just a word on pre-competitive collaboration, another place for pre-market development science to be improved. We're a party to and a convener of a number of these. And we find that there are several unique advantages to getting the industry to work together. First of all, because it creates scalable databases. And in one case we have a number of companies that have agreed to pool their control groups from their failed clinical trials and then analyze them retrospectively seeking to do things like this; build natural history of disease models and validate biomarkers of treatment response.

In addition, we also find these to be a great source of greater public and private interaction. So these pre-competitive collaborations have also been partners with the NCI, other National Institutes of Health institutes and the FDA.

Just to give you an example from the world of oncology on how these pre-market

development science improvements can work together to help us do that magical balancing act. This is a study from Walker and Newell that was published in Nature Reviews Drug Discovery back in 2009. And these are U.K. researchers who studied 974 oncology products that were under investigation, I believe, between the years of 2001 and 2007, but it might have been a wider range than that.

But what they've done is they've looked at a comparison between all drugs for cancer that were under investigation during that time period. And in the blue bars kinase inhibitors or targeted cancer therapies which were the biggest class of targeted therapies during that timeframe.

And what they're showing here is the transition probability for success from each of the indicated phase to the next. So from Phase 1 to Phase 2, almost an imperceptible difference between the targeted cancer therapies and all other cancer

therapies. From Phase 2 to Phase 3 the notoriously difficult hurdle for these therapies, you can see a dramatically higher rate of success for the targeted therapies. Same for the Phase 3 to registration and from Phase 1 to registration. Almost three times the rate of success.

Now what do the investigators conclude from this pattern? Well, they conclude, and I'll just read it to you, "that factors underlying this improved transition probability are likely to be related to the targeted nature of the molecules and to the improvements in clinical trial design such as biomarker-driven patient stratification."

The fact is that there's a lot of pre-development basic science that goes into the development of targeted therapies. And when those resources are invested, and we understand the disease mechanism and then can build products to target it, we have much higher rates of success and the products can

reach patients more efficiently. And that then is one of the great examples, and probably the first of this kind of drug development technology.

So now I'm going to move to the post-market side, that second blue box that I showed on the seesaw.

Post-market surveillance certainly has the possibility of helping reduce uncertainty about safety. As many of you know, the pre-launch data that FDA has had at its disposal in the past, mostly clinical trials, have provided only a very narrow view of the risks and benefits of treatments. The clinical trials weren't studying patients long enough to observe long term effects. They typically don't involve large enough populations to help us find rare adverse events. And the participants in those clinical trials don't represent the population of eventual users.

On the other hand, we had

spontaneous adverse events, or the AERS system, which also wasn't sufficient for drawing valid inferences around product risks because we don't have the denominator of exposed individuals. All we have are the case reports submitted to the agency.

We also have incomplete and often potentially biased numerators in those calculations, or information about the cases.

So, as all of you know in FDAAA from 2007, the agency was authorized by Congress to develop a new post-market surveillance capacity, and that's the Sentinel Initiative. Now again I'll say that Brookings has been involved in a cooperative capacity with the FDA to help think about the design of Sentinel. And what I'm sharing now are some of our perspectives on the path forward for development of post-market surveillance capabilities.

So the Sentinel Initiative, of course, will be designed to use existing

databases in a distributed network to do three things:

First, identify potential signals.

Second, strengthen those signals in the database that gave rise to them, and, then,

Third, lead to the confirmation or refutation, the hypothesis testing around those signals.

So those three steps come from a Brookings-convened methodology work group from last May. And we see those as sort of three discrete areas of safety science that the Sentinel Initiative could help address in a sequential process.

Now, we've also done a fair number of discussions and meetings with the stakeholder community more broadly. And through those discussions we've arrived at a six point implementation framework that, as I said, has been formed by this collaborative, very transparent set of discussions. And I'm

going to provide a website at the end here for anyone who would like to go back and find papers and proceedings from these meetings.

But the implementation framework is as follows:

So the first step is the data. If we're going to have an effective post-market surveillance strategy, then we have to understand the data types and data sources that can provide answers to the questions of interest. Not only that, but we also have to have a mechanism of providing incentives for the holders of that data, who might be insurance companies, who might be academic centers, who might be registries, who might be the regulated industry, to participate in the Sentinel Initiative.

The second piece of the implementation framework is network infrastructure. So we have a variety of types of data and then we have a variety of holders of data for any given type. So we have to find

a way to link all of them together. And the model, which I'll show you a schematic of in a moment, is a distributed network for information infrastructure. And that basically would create a central coordinating center to which FDA could transmit a query and then the coordinating center would work with the various appropriate data environments for any given question.

The third piece of the implementation framework is signal detection and evaluation methods. I just mentioned the three types of methods up above, but this is safety science that is not in every case perfectly well developed. And so continued methodological development is needed. We're fortunate enough to have three or four decades of pharmacoepidemiology methods at our disposal. But those have predominately been focused in this area and perhaps a little bit in signal strengthening, but we have a long way to go in understanding the best ways to

identify signals from large data sets where there's an incredible potential for false positives.

The fourth area is legal and privacy issues. It'll obviously be important, when large amounts of data are used for surveillance like this, to be compliant with HIPPA and other federal and state privacy laws. And we recently held a workshop on that, and I'm pleased to report that according to the very diverse and broad group of privacy lawyers and advocates that we had in that room, it appears that there is a path forward here that will make this very practical and feasible.

The fifth area is interpretation and communication of the results. So once we have multiple answers to a question, how do those answers get interpreted, how are they interpreted in light of what we already knew about a potential signal from clinical trials, from spontaneous reports and from the

literature? And then how is that communicated to providers and patients in a way where we balance the risk of communicating results too soon, potentially a false positive that could cause patients to stop treatment versus communicating to patients and providers too late, in which case we could potentially be exposing people to harm unnecessarily.

And then finally, governance and other uses. There's a lot of interest among not just the regulated industry, but academic researchers and others in making the Sentinel system a national resource for safety science, and not only safety science but also for comparative effectiveness research and other kinds of evidence development activities. And there are important questions about how that could be done while still preserving FDA's primacy as the organization with priority uses of the network.

So here's the quick conceptual model of the distributed data network. As I

said before, there is a coordinating center. The idea is that all of these data environments which would include inpatient data, warehouses, payer claims data, registries and inpatient EMRs, those databases stay behind their owner's firewalls. Patient level identifiable data is never transferred to the FDA or its coordinating center, but rather queries come from the FDA to a coordinating center about a specific product outcome pair. Those queries are transformed into analytic code, which is then transmitted to each of the participants depending on whose datasets are appropriate to answer the question.

The code is run on an image of each data environment's dataset and all that comes back to the coordinating center are aggregated results, in essence, the answer to the question -- how many patients were exposed, how many had the outcome and what's the relative risk or odds ratio.

The coordinating center's job is to aggregate the results they received from all the participating centers and then transmit that back to FDA.

A number of implementation pilots are underway. I won't go into detail on these because the FDA is well aware of each of them. But they include the observational medical outcomes partnership, the ten prior FDA contracts from 2008 to 2010 on a variety of topics. These were small building-block-type contracts that put certain bits and pieces of information together so FDA could build its path forward to mini-Sentinel, which is the larger contract with Harvard Pilgrim Health Care as the first coordinating Center, which will be doing what the big bubble here does in a pilot capacity testing data environments, testing methods for signal detection strengthening and hypothesis testing. It's doing work with the federal partners including CMS, CBC, the VA, the Department of Defense.

And then also its cooperative agreement with us at the Brookings Institution.

There's a lot more detail on all these topics that I'm speeding through at our website, which is brookings.edu/health and then the medical product safety suffix you see here.

So, in summary, we think it's important and possible to improve both the speed to market and our confidence in the risks and benefits if we take a new approach in investing in new tools and methods for both pre-market development science and post-market surveillance.

The practical reality, though, is that this requires more staff and more expertise at FDA which in turn requires more resources. So it's going to be also very important that there be partnerships. Working in partnership with the stakeholder community is going to be critical to the effectiveness of these initiatives in achieving the right

balance on our seesaw.

On behalf of Brookings, thank you again for the invitation to be here today. And we look forward to working with the FDA in the future on these very important topics.

(Applause.)

FACILITATOR TOIGO: Thank you, Dr. Benner.

And our last speaker for this session, Dr. Rebecca Kush from CDISC.

DR. KUSH: Thank you very much. I'm pleased to be here today on behalf of the Clinical Data Interchange Standards Consortium. And as we've all been hearing today, and as we all know, the information from health care that we use for clinical research needs to be fed back into the health care system in a way that they can make clinical decisions better. And this is a particularly inefficient cycle that we're all trying to speed up. It's been purported to take approximately 17 years.

So CDISC's mission is to develop and support global platform independent data standards to improve medical resource and related areas of health care. And in this regard, we are a multi-disciplinary global vendor-neutral open standards developing organization or SDO.

And we were founded in 1997 as a volunteer organization incorporated in 2000. The membership includes academic, biopharma service technology providers, and others.

We do have a liaison status with ISO, the technical committee that is dealing with health care standards, and that means that our standards can be taken in at a fast track level.

And we've had a charter agreement with HL7, the health care standards organization since 2001. And we are a member of the Joint Initiative Council for Global Harmonization of Standards.

We're also members of the ANSI lead

ISO Technical Advisory Group into ISO.

And we have organizations around the world. And we have established a set of global industry standards to support the electronic acquisition exchange, submission and archiving of data to streamline biomedical research.

So we have right now a suite of standards that's been completed that's available. And the initial one that we worked on was with and in conjunction with FDA since the early 2000s. And that is a study dated tabulation model that takes all the data collected from the various clinical studies and tabulates it in a way that, as you heard Dr. Sharfstein say today, can be submitted as raw data to the agency for review.

And there's also a standard for the analysis data sets. Those were developed in conjunction with and partnering with FDA and with the e-submissions in mind for analysis and reporting.

We also have a lab data standard that is from Central Laboratories that includes pharmacogenomics data. And as part of the Critical Path Initiative, Dr. Woodcock initiated a project in this regard to if you're going to submit data to the FDA, why not collect it in that standard format. And that is called CDAS, or clinical data acquisition standards.

And we now have a protocol standard that's upstream from the process to allow people to create a study design so that the FDA can look at the study design plan and compare the actual data for that.

And these are all transported through either the DCISC transport standards or some of them have HL7 transport standards. And they're harmonized and integrated with a model that has been collaboratively developed with FDA, HL7 and the National Cancer Institute. And now a number of others at NIH. And we use control terminology.

In a study that we did in conjunction with PhRMA and also Tufts and Gardner we looked at the time and cost savings of using these standards. And as you can see, this is for the non-value added time, the non-patient participation time that's the study startup and the analysis and reporting of that data, the part that you can control. And there's a significant cost and time savings. And that happens in particular if you use the data standards upstream when you're using the data collection. And these are more nonquantitative values of standards:

That they increase data quality, they allow the data integration that you need across studies if you're going to compare or do comparative effectiveness;

They facilitate exchange of data amongst different partners;

They enable a choice of different tools as long as the tools comply with the standards;

They actually improve communication amongst project teams, and they were created with an end goal to facilitate regulatory submissions and also audits at regulatory sites.

So in working with the FDA reviewers because we're now doing some training of these standards with the review teams, and also at the FDA's Computational Science Center Meeting that was held a couple of weeks ago here in Bethesda. We find that not all submissions are going in an electronic format. In fact, depending on the type of submission it may be half or more are not in electronic format.

Electric submissions are not all using the data standards consistently.

And the tools that improve review for quality and efficiency of those reviews require that data be in standard formats if those tools are going to be applied. So even answering some very simple questions can be

difficult and time consuming for a reviewer when the data are not readily accessible if they're not comprehensible, if they're not analyzable, if they're not in the standard format.

These are some issues on the end of adoption of these standards for e-submissions. So there is adoption of these standards to some degree, and I have slides on those but I didn't put them in today because of the time limit. But to date there's no requirement for standard data format. So what you find is that when asking reviewers how many submissions have been made using this standard, they can't actually tell you that because of the lack of compliance to the standard by some who are providing the submissions.

So there's also little feedback that's coming back towards the industry and especially to CDISC on the compliance or the reviewer needs. We know they just basically,

they do their best and review what they receive. They don't try to analyze the compliance to the standard.

There's a lack of clarity in what can best help the reviewers in terms of facilitating their reviews.

There is a perception by some that transport standards can solve content issues. That isn't the case. We still need good content and content standards.

And there's a perception by some that you can collect the data anyway you want and then map it to the standard at the backend of the process. And that is clearly not very easy to do because you may not have collected the data the way that the standard requires it to be submitted. So you're trying to shoehorn data into a standard when you didn't collect it right in the first place.

So we did a survey, and the data are still not quite analyzed, but I pulled out three of the questions to show today because

we just finished this survey a couple of weeks ago.

And this, as the respondent list, it's a global group of 641 respondents to this survey covering a number of different types of organizations. And when asked: Please indicate the challenges to your either initial use or continued use of the standard for FDA submissions, choose from the following or answer other. And we haven't analyzed all the others yet, but you can see that the top three are:

Implementing SDTM currently lacks clarity. So we've clearly even though we have a 375 page implementation guide, that's not enough clarity because there are certain things that people interpret different ways. So we need to have, what some have said, "The Dummies Guide" to how to implement this. But we really need more clarity in what the FDA needs to see and how we should be implementing this standard.

People are still trying to fit, like I said, data into the format and that's difficult if not impossible sometimes. And there's lack of experience.

How can CDISC assist the industry to adopt the standards better? The top one was clearly work with the regulators to provide greater clarity on what it is they want and how we can facilitate their reviews.

Provide more studies.

And also because our standards are right now limited to all of the safety data sets, 18 different domains including demographics and all sorts of different things. But we haven't done the little bit around each efficacy data set for each therapeutic area. And that's what we're working on now, but it's time consuming, it's costly and we need to develop those more.

And if you look at the positive experiences people have had:

It does improve data quality;

They gained valuable experience for the next time around, and;

It improves in-house data processing.

So those are positive gains on both sides.

So I'd just like to say that when CDISC goes and recommends thing to the industry we say please get involved, understand the standards, adhere to the implementation guides. Also discuss the data requirements with the FDA reviewers, which means that they have to start holding meetings with these companies earlier on in the process to make sure that the data are collected properly.

Use CDAS with controlled terminology.

Use electronic source, because that's what's coming in. With all that we heard of Obamacare we're rolling out electronic health records throughout the

nation and it would be better if we could collect data electronically and not transcribing it onto paper patient report forms and then reentering the data. So that would improve the efficiency dramatically.

And also, we have now a protocol representation standard that is available. And what this is does is that info for trial registrations, that's for clinicaltrials.gov or the EudraCT database in Europe, or the WHO Clinical Trial Registry. It's also the basic information that's needed in SDTM when it goes to the reviewers.

Eligibility criteria, study design and those things can be done in a protocol standard and then used again in the SDTM standard. So it can allow for efficiencies. And if you use CDAS with the case report forms, that can flow right into the SDTM dataset. So that allows for information reuse and improved quality and efficiency. And this is actually just rolled out, but it has been

in progress for the last six years because it's rather complicated, but people can see that it was coming and it incorporates a lot of the other data standards into this.

And to complete this presentation, I'd like to make three recommendations for the reauthorization in PDUFA.

One is we'd like to have more feedback on standards compliance issues and standards needs. And we need more support for standards development.

It's interesting that people will fund a lot of things that are expected to be interesting in terms of better therapies, but the infrastructure doesn't get funded. So there's no government funding for standards development. And that's an issue.

And then provide additional reviewer training and tools for sponsor communication on the use of CDISC up front so that it's done early in the process so that it not only improves processes for researchers,

but also for the FDA.

And then we really need a clear specification of direction and timeline from the FDA in terms of data standards and regulatory submissions, a plan if you will.

So that's what I'd like to close with. Thank you.

(Applause.)

FACILITATOR TOIGO: Thank you.

Any questions for this panel from our listening panel? No? Okay.

Well then I lose because we're behind. So this is the first time we're behind today, but we'll still get out early because we don't have a lot of people signed up in the open session.

So we'll take a 15 minute break and be back at 3:10.

(Whereupon, at 2:53 p.m. off the record until 3:12 p.m.)

FACILITATOR TOIGO: Our last panel is Panel 6, and for this panel we're going to

hear three perspectives from the regulated industry. Dr. Wheadon is going to speak for PhRMA, Andrew Emmett is going to talk to us about the BIO perspective and Bridget Elis is going to speak from the perspective of the Plasma Protein Therapeutics Association.

So, Dr. Wheadon, if you can start us off.

DR. WHEADON: Thank you.

The Pharmaceutical Research and Manufacturers of America, better known as PhRMA, appreciates this opportunity to respond to the FDA's request for comments on the overall performance of the Prescription Drug User Fee Act and to endorse a reauthorization of PDUFA in 2012.

PhRMA is a voluntary, nonprofit association that represents the country's leading biopharmaceutical companies which are devoted to inventing medicines that allow patients to live longer, healthier and more productive lives.

PhRMA supports a strong, vibrant and science-based Food and Drug Administration. Discovery, development and delivery of innovative medicines to patients is the core mission of our members. And this goal is further supported by an FDA that advances the public health by providing timely, scientifically sound regulatory decisions.

PhRMA was an original supporter and participate in PDUFA beginning in 1992.

As you know, FDA has requested comments in conjunction with this meeting concerning two questions:

(1) An assessment of the overall performance of PDUFA IV thus far?

(2) What aspects of PDUFA should be retained, changed or discontinued to further strengthen and improve the program?

From PhRMA's perspective, the increased focus on patient safety and post-market surveillance under PDUFA IV is the

right thing for patients. It is working and should be retained. However, implementation of certain provisions under the Food and Drug Administration Amendments Act of 2007, better known as FDAAA, particularly risk management and mitigation strategies has led to a breakdown in FDA's review process and has eroded some of the positive progress derived from earlier PDUFA agreements. New, more efficient systems and processes are required to address this breakdown in order to deliver safe and protective new medicine to patients without unnecessary delays.

In approaching PDUFA V more transparent science-based standards with benefit risk assessments and drug approvals are needed. These standards need to be consistently applied across the FDA and communicated clearly.

Additionally, FDA staff must be given resources for carrying out their jobs and training which allows them to perform

their critical task efficiently and effectively.

Governance and accountability within the agency around efficiencies, processes, timing and outcomes will be paramount to success.

Our remarks today will expand on these responses.

One of FDA's most critical functions is to protect the public health by assuring the safety, efficacy and security of human drugs and biologic products. Another is to advance the public health by helping to speed innovations in medicine.

America's biotechnology and pharmaceutical companies are committed to serving the public health. We do this by researching, developing, manufacturing and delivering innovative safe and effective medicine to treat devastating illness such as cancer, diabetes and Alzheimer's Disease. As you are aware, these activities require

significant investments of time, money and talent.

In 2009 biopharmaceutical companies invested an estimated $65.3 billion in the research and development of new medicines, up from $63.7 billion spent in 2008.

More than 2900 medicines are being tested in clinical trials or are being reviewed by FDA today. Up from 1800 in 1999.

Only one out of thousands of promising molecules makes it through pivotal trials to the patient. This attrition rate is one of the reasons that R&D costs are so great in our industry. But we assumed great risk in hopes of bring great benefits to patients. It follows then that our industry has a huge stake in doing whatever we can to facilitate timely approval of safe and effective innovative medicines to address medical needs of patients.

PDUFA has played a critical role in helping the FDA become more efficient in the

regulation of safe and effective medications. PDUFA was created in response to a perilous bottleneck of new drug approvals in the early 1990s that left patients waiting, and in some cases dying, while an under staffed and under funded FDA struggled to review new drug applications.

In 1992 Congress passed the first Prescription Drug User Fee Act to meet urgent patient demands for more timely approval of life saving medicines. For nearly 20 years PDUFA has helped the FDA to fulfill its central mission, namely to promote and protect the public health and safety by allowing the agency to keep pace with the rapid increase in the number and complexity of drugs and biologics entering the review pipeline.

The PDUFA program has enabled FDA to hire additional staff to review applications for new drugs and biologics. In 1989 FDA's human drug review program was staffed by 1,913 employees. By 2007 the review

staff had grown to nearly 3,000.

The infusion of user fees to support the FDA's review process has meant that the median time to review a new drug application or biologics license application has been reduced significantly, from 29 months in 1989 to 13 months in 2006.

Priority review products, drugs that offer major advances in treatment or provide a treatment where no other adequate therapy exists, now see a median review time of just six months.

The NDA review process has also become more efficient as a result of PDUFA. When PDUFA was first enacted in 1992, FDA approved 46 percent of priority new molecular entities during the application's first review cycle. By 2007 this percentage had increased to 74 percent.

The beneficiaries of PDUFA are the tens of millions of Americans who rely on innovative medications to improve and extend

their lives. In fact, PDUFA has resulted in patients having earlier access to more than 1,100 new drugs and biological medicines across many therapeutic categories.

In the 2007 reauthorization of PDUFA important new safety-related elements were incorporated into the user fee legislation. User fees to support drug safety measures totally $225 million were added. And in addition, previous statutory time limits on close approval activities were lifted enabling FDA to use PDUFA funding for regulatory activities throughout the life of a drug and biologic.

Furthermore, the list of post-market safety activities for which PDUFA fees could be used was expanded to include adverse event data collection, the development of improved tools for assessing potential safety problems and implementing and enforcing new regulatory authority to require post-approval safety studies, new clinical trials, labeling

changes and REMS.

Some critics have suggested that the adoption and subsequent reauthorization of the PDUFA user fee program resulted in weakening safe FDA safety standards and/or oversight. However, this has not been proven to be the case. In fact, additional funding provided under PDUFA III and IV has FDA to ensure patient safety more effectively by extending surveillance of new medications into the post-market period.

It's important to keep in mind that PDUFA user fees have provided and continue to provide the FDA with the critical resources necessary to expedite access to new medicines for patients in need. FDA's chronic shortage of appropriated funding has been well documents. While this critical public health agency regulates $1 trillion of consumer products, 25 percent of the U.S. consumer economy, it's federal appropriation in 2007 was only $1.57 billion, less than 75 percent

of the budget for the Montgomery County Maryland Public Schools.

Put in another context, FDA's appropriated budget of $2.4 billion in fiscal year 2010 pales in comparison to other federal agencies charged with protecting and enhancing the public health. The Centers for Disease Control and Prevention received $6.5 billion in appropriated funding in fiscal year 2010, and NIH's budget increased to more than $31.2 billion.

Clearly, while PDUFA user fees have served to augment appropriated funds to help the FDA keep pace with other public health agencies, they are clearly no substitute for adequate appropriations to resource the agency to fulfill its critical public health mission.

Despite the clear progress that has occurred under PDUFA I, II and III there are signs of drift away from the original intent of PDUFA bringing innovative new treatments and life saving new medicines to patients

faster. FDA itself has conceded that its ability to review new drug applications in a timely manner has decreased by the addition of new processes and the implementation of the requirements in FDAAA, particularly REMS.

A recent report found that 40 percent of the priority of the NDA, BLA submitted in fiscal year 2008 has missed user fees goals. Sharply up from 14 percent for the fiscal year 2007 cohort.

Of even greater concern for industry, FDA states in its report, those overdue priority applications have a higher first cycle failure rate. Of the fiscal year 2008 priority NDA's on which CDER had taken action as of April 2009, only 50 percent were met an approval, the lowest rate since the fiscal year 2001/2003 period.

Systems and processes must be in place to allow FDA to access effectively the safety and efficacy of new medicines, including strategies to mitigate risk and

enhance benefit while adhering to the timely goals that have marked FDA's under previous PDUFA programs.

PhRMA will continue to serve as a constructive partner with FDA working with the agency on review processes to help ensure that new medicines are safe and effective. This includes building new mechanisms to ensure that the various offices within FDA work together seamlessly and more effectively.

Some basic principles that should guide a reauthorization of PDUFA include:

A focus on advancing public health while sustaining continued progress and developing and securing access to new medicines;

Ensuring transparent science-based review and approval standards for efficacy, safety, manufacturing and post-market obligations;

Providing FDA with adequate resources, personnel and staff training

opportunities and advancing regulatory science by augmenting the ADC scientific base, and lastly;

Ensuring the best use of FDA resources through enhanced management, governance and regulatory accountability focusing on processes, appropriate timing and outcomes including greater clarity around the role of Office of Surveillance and Epidemiology and improved functioning and processes for FDA advisory committees.

By focusing on these principles PDUFA IV can play a critical role in making more innovative medicines available to Americans in need by continuing to put safety first and by renewing FDA's commitment to move new medicines through the approval process as quickly as prudently possibly.

Both the FDA and makers of medicines have vitally important responsibilities to safeguard and improve public health. It is our shared responsibility

to ensure that America's health care system stays at the forefront of quality and innovation. Supporting the FDA's ability to perform in this critical review and subsequent monitoring of new medicines in a timely and efficient manner is one way that our industry can continue to serve patients.

The ultimate review and approval process is one that is both efficient and judicious. Public health and safety are best served by a science-based balance between the need for timely and rigorous pre-market review and post-market surveillance.

Through its history PDUFA has allowed the FDA to move closer to the appropriate balance, which is why we vigorously endorse a reauthorization of PDUFA in 2012.

Thank you.

(Applause.)

FACILITATOR TOIGO: Thank you Dr. Wheadon.

And Mr. Emmett will speak for BIO

MR. EMMETT: Good afternoon, everyone.

On behalf of the Biotechnology Industry Organization, I thank you for the opportunity to comment in support of the reauthorization of the Prescription Drug User Fee Act and to discuss how we can ensure achievement of the goals envisioned under PDUFA and make further refinements to that end.

BIO represents more than 12000 biotechnology companies, academic institutions and state biotechnology centers and belated organizations across the U.S. and in 30 other nations.

Innovations in health care including new therapies, vaccines and diagnostics has been and will continue to be central to an improved health care system and a key driver of economic progress. Biotechnology has created more than 200 new

therapies and vaccines, including products to create cancer, diabetes, HIV/AIDS and autoimmune disorders.

There are more than 400 biotech drug products and vaccines currently in clinical trials targeting more than 200 diseases. Recognizing that a reliable, science-driven regulatory environment fosters innovation and promotes economic competitiveness and maintains a high patient confidence in the integrity of medicines, BIO member companies have supported a carefully structured user fee program to help fund FDA's human drug review activities.

PDUFA has been widely credited as an innovative program that has strengthened FDA's capacity to evaluate expeditiously and efficiently the safety and effectiveness of new drugs and biologics.

Since its inception in 1992 PDUFA has helped enable FDA to approve more than 1,100 new medicines and reduce review times

for innovative drugs and biologics, thereby providing patients and doctors with earlier access to breakthrough treatments.

While overall the PDUFA program has been a success, there have been recent slippages in FDA's performance which deeply trouble BIO's membership.

Three subsequent reauthorization of PDUFA, the user fee program has been refined to further help achieve a full life cycle approach to product evaluation. To help promote biomedical innovation industry user fees are intended to provide FDA resources necessary to meet with sponsors and provide scientific and regulatory advice during clinical development.

Under PDUFA IV industry reinforced its commitment to drug safety and strongly supported an increase in user fees and the application of user fees to enhance and modernize FDA's post-market safety and pharmacovigilance activities.

As we look ahead to the upcoming reauthorization of PDUFA, we must critically evaluate the program.

Have drug applications reviews become efficient?

To what extent have the user fee program or user fees contributed to that?

Have there been unintended consequences that may have undermined the original intent of the program? For example, are PDUFA review goals successfully speeding new medicines to patients or are the goals simply being treated as work load management tools?

Why have significantly increased investments in the PDUFA program in recent years realized only marginal enhancements in the drug program?

Before considering changes to the PDUFA program as part of the reauthorization process, it's important to discuss the appropriate role and fundamental limitations

of a user fee program and what can and cannot be addressed in the PDUFA commitment letter.

First, we must reinforce that PDUFA is about providing additive resources to hire staff for human drugs and biologics reviews to promote efficient performance management and application review process.

PDUFA is not about revisiting FDA policy or revising FDA's review standards.

Second, it's commonly said that you get what you measure. And we believe that continued utilization of PDUFA performance metrics will track ongoing program progress and assure accountability and transparency to the public.

The user fee program supports FDA's ability to make a science-based empirical judgment in an appropriate time frame and in no way presupposes the outcome of that product review, whether it be an approval or a complete response letter.

Third, user fees by definition are

fees paid by the user for the benefit of the user. Biopharmaceutical companies pay application, establishment and product fees because they benefit, as does the public, for more efficient reviews, timely scientific advice and ongoing product evaluation.

Newer medicines are increasingly more complex and FDA needs the appropriate level of scientific training and review quality to fully evaluate the benefits and risks of the products. This ultimately benefits U.S. patients by making decisions on applications earlier and allowing for safe and effective drugs being made available to the American public in a timely manner.

The larger missions of responsibility of FDA to ensure and improve the public health for the benefit of all citizens should be funded by the agency's appropriations, not by a specific part of the FDA regulated industry.

Indeed, user fees were never

intended to supplant a sounds base on FDA appropriations. BIO continues to be concerned that the appropriative based of the human drug review program has not kept pace with its needs and work load. In fact, in FY '08 two-thirds of the overall cost of human drug review was supported by industry user fees. This over relying on funding collected from the industry FDA regulates undermines public confidence in the agency's objectivity and creates the misperception that FDA's beholding to the industry it regulates. In the long term, this perception is not in the best interest of patients, biopharmaceutical innovators, or the FDA.

The solution to this is to increase FDA's appropriations for human drug review to meet the agency's program needs. We applaud Congress for recognizing the importance of FDA in increasing the agency's budget by nearly a billion dollars over the last three budget cycles. But we respectfully suggest that even

with these increases funding is still not adequate to assure that FDA has sufficient resources to carry out effectively its continually increasing responsibilities.

We look forward to working with Congress to ensure that FDA receives additional appropriated funding so the agency can keep pace with biomedical scientific discovery, modernize its regulatory tools and scientific capacity and respond to the challenges of regulating in a globalized economy.

In part, our work to achieve that goal will be done in conjunction with and as a founding member of the Alliance for a Stronger FDA, a coalition of 180 organizations representing patient groups, consumer advocates, medical societies and regulated industry.

While BIO continues to support increased FDA appropriations, we also believe that FDA should justify how increases in

resources have contributed to advancing the agency's public health mission. To demonstrate that FDA has been a responsible steward of both industry user fees and public appropriations, we urge that FDA transparently document how funds have been allocated internally and clearly explain the performance gains and public health improvements achieved through these increased funds.

For example, between FY '07 and the proposed FY '11 budget, PDUFA user fees have more than doubled from $320 million to $667 million. And appropriated budget authority for the Human Drugs Program has increased by almost 170 million. How have these increased resources been distributed within the agency and the Office of New Drugs, and what measurable increases in FDA performance have been achieved with this funding?

BIO supports the reauthorization of PDUFA, but believes that future modifications to the program must be justified by robust

data. At this time we're only half way through PDUFA IV. It seems premature to evaluate the changes made in the last reauthorization, since there's only limited data available on which to base an evaluation. Applications cohorts have not yet fully matured. PDUFA financial and performance reports have not been publicly released. And the accelerated time frame to begin consideration of PDUFA V means application review data and other performance metrics are available for only two years, rather than three years in which previous reauthorizations were based. However, preliminary data that has been publicly released by FDA suggests that the agency has been struggling to meet its PDUFA goals.

In FY '08 FDA fell far short of the 90 percent application review goals, even for products representing a significant public health advances. For example, FDA acted on only 60 percent of priority NDAs and new BLAs

within six months and 71 percent of priority NDAs and BLAs. This drop in performance may be due in part to a lag in recruitment that coincided with additional work load from implementation of the FDA Amendments Act of 2007. Consequently, OND opted to triage their work load and granted reviewers permission to disregard its certain PDUFA commitments. By the summer of 2007 an average of 25 applications per month work was overdue, up from the low single digits in early 2007.

While FY '08 and FY '09 data may not be representative of the full potential of revitalized human drug review program with increased staff and resources, BIO was deeply troubled by the current trend lines and we note that this clearly illustrates the difficulty of evaluating the program with a limited dataset.

We recognize that as with any large organization period of significant growth and excessive work load can contribute to

organizational disruption and decreases in efficiency, and these factors should be carefully considered when considering the future regulatory changes. However, the dependability of FDA's good faith adherence to the established performance goals is one of the critical underpinnings to sustaining the PDUFA program.

To generate additional information to inform the reauthorization process, BIO surveyed its membership to collect information about their experiences under PDUFA IV and identify areas for improvement and refinement under PDUFA V.

Sixty-eight BIO members participated in the survey, a strong indication of a high level of importance attached to this topic. And represented an equal cross-section of BIO's large, medium and smaller companies.

The survey is not scientific, but provides valuable insight on industry views.

First, the bad news. When asked if the performance if the FDA Human Drug Review Program has increased, decreased or remain the same since the start of PDUFA IV in 2007, 53 percent respondents indicated that FDA's performance has decreased while only 11 percent have seen improvements.

The survey further identified several areas where there may be room for future improvement and opportunities to further integrate new FDAAA statutory requirements into the drug and biologics review and evaluation process.

For example, one of the most significant changes under FDAAA was the codification of first evaluation and mitigation strategies or REMS. Best Practices has demonstrated that it's critical that FDA sponsors have a common understanding of when and how sponsors should communicate with FDA regarding potential REMS, and how that discussion should be integrated into the

review process. However, 81 percent of respondents with REMS reported that FDA did not initiate risk management discussions early enough in the review cycle, and 77 percent reported that REMS discussions contributed to a review extension.

BIO believes that it's important to revise FDA's review processes so that REMS, post-marking requirements and other FDAAA related discussions occur earlier in the review cycle.

Multiple review cycles caused by REMS may be, in part, symptomatic of suboptimal internal communications at FDA. For example, 61 percent of survey respondents reported inadequate coordination between the Office of New Drugs and the Office of Surveillance and Epidemiology during product reviews.

We'd like to better understand the interactions between OND and OSE and how different safety interpretations are resolved,

both internally and with external stakeholders.

In addition, meetings and communications between FDA and companies early in the development and review process is crucial to the advancement of new cures. In fact, the 2008 independent analysis by Booz Allen Hamilton found that early and frequent FDA sponsored communication contributes to higher first cycle approval rates, which can reduce FDA's overall resubmission work load. BIO members value the opportunity to meet with FDA and staff to engage in technical expert-to-expert scientific dialogue. Yet more than half of survey respondents 52 percent, indicated that requested meetings are not being granted on a consistent basis. We hope to work with FDA during the PDUFA 5 discussions and elsewhere to identify and minimize barriers to granting formal meeting requests and to encourage opportunities for informal scientific and technical dialogue.

Next, we note that FDA's drug and biologics review processes can be inconsistent across review divisions. For example, review divisions appear to have differing informal criteria for meeting with sponsors, requesting clinical data and interacting with sponsors during the review process. This can lead to difficulty anticipating FDA's review expectations and uncertainty for sponsors.

We're pleased to see FDA managers implementing the agency's good review management principle and practices through the 21st Century review program and establishing timelines and milestones for certain sponsored FDA interactions. Although only a handful of applications have been reviewed under the 21st Century review program, survey respondents reported that FDA provided a timeline of review milestones 50 percent of time, but managed to successfully meet those milestones only 40 percent of the time.

We encourage FDA to continue to

implement and adhere to the 21st Century review program which will encourage greater consistency and predictability in the review process as part of a clear and transparent regulatory decision making process.

Finally, BIO supports FDA's efforts to recruit the best available external scientific expertise to serve on its FDA advisory committees. However, we're concerned that under new conflict of interest policies and the FDAAA waiver cap, FDA's not been able to consistently recruit advisors who have the requisite breadth and depth of experience that's necessary to provide the best possible advice. In fact, 56 percent of survey respondents indicated that FDA was unable to recruit highly qualified experts to provide scientific advice on advisory committees. This is particularly troubling for the biotech industry because the available pool of qualified experts can be quite small in certain high tech areas and rare diseases.

So in conclusion, thank you again for the opportunity to present BIO's views on the state of the PDUFA program. And we look forward to working constructively with FDA and other stakeholders to achieve the full realization of the goals of PDUFA.

Thank you.

(Applause.)

FACILITATOR TOIGO: Thank you Mr. Emmett.

MS. ELIS: Good afternoon. I'm the last person on the last panel, so I will try to go quickly. I know you see slides, but I promise there's only nine of them.

Thank you, Terry.

My name is Bridget Elis. I'm here to represent the Plasma Protein Therapeutics Associations, better known as PPTA.

PPTA would like to thank FDA for the opportunity to speak here today.

PPTA is an international trade association and standard setting organization

for the world's major producers of plasma-derived and recombinant analog therapies. We refer to these collectively as plasma protein therapies.

PPTA represents 97 percent of the U.S. source plasma collection centers in the U.S., and eight manufacturers of plasma protein therapies in the U.S.

Plasma and protein therapies are used to treat rare diseases, generally these are usually chronic, genetic, life threatening diseases that require infusions or injections for a patient's lifetime.

This slide delineates the members that PPTA represents and currently pay user fees here in the U.S. Though we only represent a small portion of the pharmaceutical industry, we believe they're important because they play a vital important role in the patient community they serve.

Plasma protein therapies are regulated through CBER and reviewed within the

Office of Blood Research and Review.

PPTA appreciated the opportunity to participate under PDUFA IV reauthorization process. We appreciated FDA reaching out to other stakeholders that had not previously been part of this process.

The openness and transparency of the PDUFA IV process provided PPTA a voice to influence the PDUFA performance goals where we had not been previously included.

We believe it's important that patients and other stakeholders be included in this process because the user fee program plays a vital role to FDA.

Overall, PPTA members are very pleased with FDA's performance under PDUFA IV. PDUFA IV time frames have been met for PPTA members and we believe there do not need to be any current adjustments to those time frames.

Areas of concern under PDUFA IV are the timeliness of data requests. These often occur at the end of the review. The

implications of these requests can be costly and difficult to manage for PPTA members. They're often not well coordinated by the agency and they come right before an action date. PPTA believes better coordination of requests and earlier communication of them to the members would be helpful.

PPTA supported the use of the good review management principles for mid-cycle reviews, but we believe they're not being used consistently right now. The use of mid-cycle reviews would allow for better communication and coordination between FDA and industry and alleviate the headache of the rush data requests at the end.

Another area of concern for PPTA members under PDUFA IV has been the expansion of user fees for post-market surveillance programs. PPTA supported the use of user fees under the periapproval phase of PDUFA III. However, we do not support the expansion of post-market programs through PDUFA fees any

further. PPTA believes post-market programs should be funded through appropriations.

Under PDUFA 5 as we move forward. User fees should supplement FDA budget. It is important that non-user fee programs receive adequate funding, and that would be congressional appropriations. Current fees are significant and further increases should be detrimental to the smaller companies PPTA represents.

This slide delineates the 1993 rate up through 2010. As you can see, they skyrocket. PPTA understands that the agency has increased costs over these years, but we are all operating in a different climate now and we have to realize that the budget has to be within certain parameters. We think it's important that the agency understand that smaller pharmaceutical companies cannot always pay these outrageous fees.

As PDUFA is expanded further it's important that the agency understand it

directly impacts these companies.

We understand that it's necessary to have these user fees, but we just want to make sure that they understand the repercussions that will happen as they go up.

In conclusion, PPTA members support PDUFA. PPTA appreciates the opportunity to speak here today. And we look forward to working with FDA under this reauthorization process.

(Applause.)

FACILITATOR TOIGO: Thank you, Bridget. And thank you to our industry panel for your comments.

Are there questions from our FDA listeners for the industry panel.

Okay. Then thank you again for participating.

Maybe if the FDA listeners can join me up here, that might stimulate some questions from our participants. Because when I checked at the break, we had one person

signed up, but that person hadn't shown up.

So here is your listeners, along with Dr. Mullin. And so this is your last chance if you want to make any comments for the FDA panel to hear.

And just to refresh your memory as to what the two questions are that we're looking for comments on, those are the questions.

Okay. So then let me -- I thought for sure when they saw the panel, we'd get some questions. But going once, twice, three times. Okay.

So I want to thank you all then for coming to the meeting and staying with us. We appreciate the input that we heard from our many diverse panels throughout the panel.

We especially thank those panel participants who took the time to review the questions and to provide us their thoughtful comments.

As I mentioned earlier, there were

a number of FDA people taking notes. So even though we weren't asking questions, you were speaking to us. The notes from the meeting were captured. We'll have a transcript. And the docket is open for 30 days. So we'll be collecting comments up until May 12th. And then we'll be reviewing them all and analyzing them, and figuring out next steps.

Congress did specify some of our next steps. Congress said that we will continue to communicate with our stakeholders no less frequently than once a month during the negotiations with the regulated industry. So you can expect that we will continue to dialogue with our stakeholders.

Again, thank you to our speakers and to our audience for your participation.

And one last word of thanks, since it takes some effort to put a meeting together like this, and there's always those people in the background that are doing those things, in addition to the people here who worked on the

agenda. Special thanks to Patrick Frey, Dan Brounstein, Mary Gross, James Valentine, Janelle Derbis, Pat Kuntze and Erica Cross for their efforts to support the agenda and all of the other meeting logistics for today. And hopefully I got everybody there.

And then finally, your feedback is important, positive and negative. You can stop me, or you can talk to any FDA staff, or you can email me your comments, your concerns, your questions. It's teresa.tolgo@fda.hhs.gov.

And unless one of our listeners has a comment, then we'll end.

Comment from Dr. Mullin.

DR. MULLIN: I just want to also add my thanks to Terry. This was a very helpful input. Extremely thoughtful and very helpful input to us as we start this process. And you've given a lot to us to start to chew on. And many of the things we've already been thinking about. And it's to me a very great

start to this process, which we have to start sooner than I suppose a lot of us would like. But to meet the statutory time frames that Congress has specified, we're starting.

So thanks very much for coming today.

FACILITATOR TOIGO: Okay. So that ends our meeting.

Thank you all.

(Whereupon, at 3:54 p.m. the meeting was adjourned.)