U.S. FOOD & DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE ACT

(PDUFA) REAUTHORIZATION

PUBLIC MEETING

July 15, 2015

9:01 AM - 2:03 PM

Food and Drug Administration

White Oak Campus

10903 New Hampshire Avenue

Conference Center, Building 22

Silver Spring, Maryland

Reported by: Natalia Thomas

Capital Reporting Company

C O N T E N T S

P R O C E E D I N G S

MS. TOIGO: Good morning and welcome to this public meeting on the Reauthorization of the Prescription Drug User Fee Act. Thank you all for joining us today.

My name is Terry Toigo and I'm the Associate Director for Drug Safety Operations in the Center for Drug Evaluation and Research, and I will be your moderator today.

Today's meeting is an important step to begin gathering input from stakeholders on features of the PDUFA program in advance of the discussions that will begin with the regulated industry. We'll continue to engage with pubic stakeholders throughout the reauthorization process and a Federal Register notice will publish in the next week with details and instructions on how to notify us of your intention to participate in this process.

We do have a full agenda for today's meeting. Dr. Stephen Ostroff, the Acting Commissioner of Food and Drugs, and Dr. Robert

Califf, Deputy Commissioner for Medical Products and Tobacco will get us started this morning with some opening remarks, and then Theresa Mullin, the Director of the Office of Strategic Programs in CDER will provide a presentation on PDUFA background and reauthorization -- and the reauthorization process.

We'll then have panels and these panels will provide perspectives from the following groups:

consumer advocates; patient advocates; health professionals; the regulated industry; scientific and academic experts. And then Dr. Janet Woodcock, the Director of CDER will provide remarks.

And as you can see from the agenda, there will be time for public comment at the end of the meeting. So if you wish to speak, you need to sign up earlier in the day and do so at the registration table, and then depending on how many people sign up will determine how much time there is for people to speak.

So each panelist today will have 10 minutes to present their organization's perspective on PDUFA. And as we do have a full agenda, we'll need to adhere to that timeframe. So it's my job to let speakers know when they're approaching that time limit and I'll be polite but when you get close to 10 minutes, I'll ask you to wrap it up.

FDA provided three questions in the Federal Register notice announcing this meeting to help our presenters prepare their comments.

Question 1: What is your current assessment of the overall performance of PDUFA V thus far?

Question 2: What current features of PDUFA should be reduced or discontinued to ensure the continued efficiency and effectiveness of the program?

Question 3: What new features should FDA consider adding to the program to enhance the efficiency and the effectiveness of the human drug review process?

PDUFA reauthorization deals with process enhancements and funding issues. Policy issues are beyond the scope of this reauthorization process. There is also a public docket open until August 15th to which the public can submit comments.

A few brief housekeeping announcements before we start. We'll have a 15-minute break at 10:40 and a 50 minute lunch break at noon assuming I do my job properly. There are food and beverages available to purchase at the kiosk outside the room in the lobby and we ask that you consider pre-ordering your lunch before 11 o'clock so that we -- because we only have a short time for lunch and we can -- that will help crowd management. And so the food and beverages, as most of you have been here before know, there's the kiosk outside the room. And then restrooms are down the hallway in the lobby on the left. So that's it for housekeeping.

We'll begin our meeting with Dr. Ostroff and to provide some opening remarks.

DR. OSTROFF: Good morning and thanks very much, Terry, for the introduction. And let me start by welcoming all of you. It's great to see such a large crowd that made their way out to White Oak and also to FDA. And most importantly, let me thank you for taking the time out of your really busy schedules to be able to participate in this meeting.

This is, of course, the first activity related to the process of reauthorizing PDUFA. I'd like to think it's a very auspicious day. When I got home last evening, I turned on the television and saw this amazing story about the fly-by of Pluto and couldn't help marveling at what an incredible achievement that was. It's really an amazing example of what can be achieved in today's world through innovation, through strategic vision, through meticulous planning and through great performance. And I'd like to think that we're in a similar era when it comes to biopharmaceuticals, although probably most of our examples are not quite as dramatic as the fly- by

of Pluto.

But over its 23-year lifespan, that other thing that starts with "P" and is five letters, which is PDUFA, has been really a great facilitator in the ability to be able to bring products of scientific innovation and biopharmaceuticals to market, to be able to improve the health of people throughout the country and indeed throughout the world in a stable, predictable and an increasingly efficient manner through strategic vision, meticulous planning, and great performance.

So just some of the examples of that: During the 23-year period that PDUFA has been in existence, the clinical development times and approval times have dramatically decreased even as the complexity of the drugs and their associated data that require review have increased quite dramatically. The public has gained access over that 23-year time period to more than 1500 new therapeutic options and today most new drugs become available first in the U.S. In 2014 alone,

41 novel new drug products were approved with 17 of these being approvals for orphan drugs, the highest annual total ever.

And FDA really continues to meet or exceed nearly all of our review performance goals that are central to PDUFA process and outcome deliverables. In addition to that, first cycle approval rates for NMEs and BLAs have been steadily trending upward towards historic levels; 73 percent of all novel products and 93 percent of priority novel products have been approved in the first cycle during PDUFA V. We'd like to believe that this is due, at least in part, to the success of PDUFA V NME BLA review program, which is an innovation from the last PDUFA reauthorization that facilitates early communication between review teams and sponsors and I think has been one of the keys to success.

PDUFA has also expanded since its inception. We now have 30 measurable review and procedural goals as well as many additional commitments to other activities including guidance

documents, public meetings, and staffing enhancements. This is an example of what gets measured gets done.

So as we enter the PDUFA VI negotiations, we have to build on our previous success to continue to make progress in our shared goals. At the same time, we should also examine whether aspects of the program can be scaled back, whether they can be modified, or whether they can be discontinued to be able to better focus on those things that are the most value-added.

So PDUFA is the grandfather of our user fee programs and serves as a bell weather of how we can achieve great things when all of our stakeholders are pulling in the same direction towards the mutual goal of making a difference to patients who need newer and better treatments. When that happens, everybody wins. So I think together, as we start the discussions around PDUFA VI, we can achieve great things. And just like the journey to Pluto, now that we've gotten to the furthest planet, and yes, to me, Pluto is a

planet, with PDUFA, it's time to build on our success and aim for the stars.

So thank you again for participating today. We look forward to hearing your ideas as the jumping off for PDUFA VI. Thanks again.

(Applause.)

MS. TOIGO: Thank you, Dr. Ostroff. Dr. Califf.

DR. CALIFF: Thanks, Terry. I also want to express my appreciation to all of you for taking the time to be here. It's really a critical exercise for us. Also, as a relative newcomer to the FDA, I just want to say that I'm actually almost overwhelmed with the importance of and the magnitude of the PDUFA process in particular. As an outsider, I knew about it. I've worked with the FDA a lot. But on the inside, when you see how working together identifying areas of mutual interest and the funding that comes with it have led to dramatic successes. It's really exciting. But I think what's been done in the past is only really a

prelude to what can be done now because it's an amazing time in biomedicine.

I also just want to take a second to thank Steve. I think a lot of you know he stepped in with very little working into this job, and I think he's handled it with pretty amazing grace and always standing up for the FDA and all the people who work here. So thanks for what you're doing here, Steve.

Also as a newcomer, I'm constantly reminded that this is a limited effort. It's focused on process, not on policy; I'm very well-aware of that. Also, knowing that as we talk about process and the things that are of interest to you, it will give ideas and things will germinate that might, in other venues, be important for us to think about.

Finally, just in terms of general comments, I think the public is increasingly aware, in a board sense, of what goes on here. User fees are an increasing part of the budget of the FDA and I think the way it's been handled in

the past going forward into the future is really a good example of how to make this work. Steve pointed out we all want to roll in the same direction where we can, but we also all recognize that we do have distinct roles in the ecosystem. There wouldn't be a need for this process if we just completely agreed on everything. So I think the way it's laid out is really exciting and interesting.

Just a few real quick points about where this is going and at least things that I see as critical from the past. The sort of combination of investment of resources and identification of opportunities is really the sort of combustible part, I think, of this process. Some people who know me well know I oft get upset at the word "process" because it sort of connotes a sterile cookbook of how to do things, and what I've learned is that's not at all the case in the PDUFA negotiation. It's a combination of those two things that leads to better ways of doing things, not just checking boxes and meeting timelines.

That's really exciting.

The effort has already led to a major increase in predictability of the regulatory effort, and I know that through the course of today and the next few months, that will be a constant thing that we'll want to continue to work on. But in addition to predictability, we want a better environment for innovators to work.

I had the chance to meet with type one diabetes groups with children who came in and told us their stories. So they want safe and effective medical products but they also want to have a chance of cure, even if it produces some risk. So developing an environment where that can happen will be critical.

Then the last thing is stakeholders. I was a little afraid of patient advocacy groups in my previous academic role until about five years ago in CTTI, which is a public-private partnership between multiple groups and the FDA. A patient advocate sort of took me aside and said, "You got to quit avoiding us. Here are the reasons you

better pay attention to us." AND it's one of the best pieces of advice I ever got. We're entering this era now where patient groups and multiple stakeholders exist in this ecosystem. We do have differences but where we can identify the common themes, this is where the real progress is going to be to be made and it's very exciting.

So we look forward to the input that we get today. I know we'll learn a lot. We always do from these types of meetings. And I want to really thank Terry and Theresa for the expert way they put this together. As a newcomer, I feel like I'm in like the greatest wise hands with Theresa, who has managed this process now for many years, knows all the tricks of the trade. So thanks again; look forward to today's proceedings.

(Applause.)

MS. TOIGO: Thank you. Theresa's going to start us off on the reauthorization process discussion.

MS. MULLIN: Thank you, Terry, and, I guess, thank you, Rob, for attributing to me

knowledge of all the tricks of the trade. Well, I guess we'll see, right? And so I'm going to -- my job is to give you some -- a quick background and this is in some ways to just maybe provide some numbers and a little more information around a lot of the points that Dr. Ostroff was making. So with that, I'm going to just give you a quick PDUFA overview, the background of the program which has been in place now since -- 1993 is the first fiscal year in which it's been operating; a little about the fee structure, so some of the mechanics because this is really kind of the stuff we would get into in terms of our discussion -- a lot of our discussion in the coming months; accomplishments to date -- we're about halfway through the program, it sunsets in 2017; and then a bit about the reauthorization process which we hope that you will continue to be engaging in.

So before the passage of the first PDUFA in 1992, you know, drug lag was a big problem. The U.S.

was behind Europe in many areas and

certainly cancer patients and AIDS patients felt that they weren't getting treatments available to patients in Europe and elsewhere, and that was one of the big impetuses for this program. So the user fees added resources to hire the review staff. We needed to speed things up, address the backlog and do all these commitments to better process that you've hearing about. The result has been a more streamlined and predictable process, tremendous dramatic improvements in terms of the reduction in time in review, and time in development, so -- and many new products have gotten to patients sooner as a result.

The way this works is that the fees are added to appropriated funds and that's a very important aspect of this because there's a public investment which is the taxpayer funder. That's the BA part of this and then their user fee funds are added to that. The fees are basically -- and by definition of the Office of Management and Budget -- providing a direct benefit to the fee payer above and beyond what is enjoyed by the

general public; and in this case, the public would all benefit from having these medicines available companies benefit from having that more timely review of their application and predictable interactions with FDA.

And so these user fee discussions we have with industry are focused on specific types of enhancements to, as Dr. Califf said, the process of the review of human drugs. We look at specific enhancements to that review process and those interactions in development and then during review and say well, what is technically feasible that we could add; what would it take; what level of effort is required to really carry that through for every sponsor who may want to have that service or that timeframe met; and is that something that is doable financially? And there's no discussion of policy so it really focuses around these process issues. And getting those process specifications right because they have financial impacts, it's very important that we are very clear about what those process specifications

are so we say the devil is in the details.

This is just a brief history -- I won't go through it -- but to show you that each one of these efforts actually has had a slightly different focus. There's always been a bit of a theme. The first time we -- the program was enacted, it was to address the backlog and begin to institute these timeframes in a managed review process, which was a new concept for FDA. And we since then incrementally improved upon it. The next iteration of PDUFA included goals for meetings and so that meetings during the development phase could be more predictable and companies would be able to come in and seek FDA advice during development in a more predictable manner.

Subsequently, we added postmarket safety funding. By PDUFA V, we removed any restriction on the ability to follow drugs throughout their life cycle when they're on the market when new safety findings may arise.

And finally, we've focused more in this

most recent iteration on adding regulatory science initiatives and particular ones that patient stakeholders identified during our process of consultation with them during the last reauthorization effort. And so we added those and other enhancements. So, for example, we can get electronic submissions in. That allows us to do more sophisticated analysis during the review.

This is just a quick overview of the fee structure. There are three pieces -- three components of fee. It's divided into a full market application, payments, establishment fees for the finished dosage, foreign facilities, and product fees. The total revenues in this current fiscal year are estimated to be on the order of $800 million dollars, and that last is just a breakout of those -- the amount of fee per submission or per item in the current year, so it's a big program.

This is an example of how the goals are structured. I won't go through it but as you can see, for each type of submission or action of

review, an FDA commits to a complete review within a timeframe, not what the answer will be to that review but just that the process, 90 percent of the time, not 100 percent of the time because there are always exceptional cases, so we try to -- - we aim for the 90 percent for these types of items. And as Dr. Ostroff said, there are over 30 such goals.

This chart, and I'm sorry, you probably cannot read this. No, you chant read that. Okay. The dark blue bars on the left are how many submissions that -- I mean I'm sorry, that's the performance goals. So the red line is 90 percent and so you can see that we're meeting or exceeding in those cases the goal to complete that process in that timeframe. And the bars on the right, the light blue bars are how many submissions that we've got related to that goal. So it's -- there is a lot of freight moving through this process. You might say lots and lots of volume of work.

Now in order to meet those timeframes, we have a large integrated review team with

multiple scientific disciplines need to be involved. So the pink part of the bar you see here is the internal goals that we set to modulate and have this process that's complex but needs to be because the products are becoming increasingly complex in order to orchestrate this to get a final decision or to get the external goals met. So all told, we have -- our reviewers are following as an organization on the order of 16,000 goals in order to just keep moving things along and getting that complete process with all the necessary input and vetting in the timeframes that we've committed to. So there's a lot of organization that goes on behind the scenes to make this happen.

I'm going to give you a quick recap on PDUFA V. In addition to this new review program that Dr. Ostroff mentioned, and I'll say a little bit more about that, we had a number of scientific -- regulatory science initiatives listed there. I'll go through in a minute. We're midway through it and we can say a little bit of what we've done

to date.

And so first of all, the new -- the NME program for -- I mean the new review program from the New Molecular Entities and UBLAs added two months to the review clock to allow us to do a filing review and then increase the communication during the review process in some very key points in the review process that were identified. And this has been extremely helpful even with the two months addition, as you can see on the right side of this chart, the median time to action is just about exactly two months more because the review timeframes were pushed out two months. But on the left, what you see is this additional communication and it has enabled applicants working with FDA to work toward approval in the first cycle. In some cases, that additional communication has enabled the companies to bring additional information to the table or address issues that could be addressed in the first cycle. And as a result, we have over 50 percent first cycle approval rate for the standard NMEs that

have come in and over 90 percent approval on the first cycle for the priority applications, which is historically high I would say.

We've had -- for some of these other initiatives -- I'll try to go through quickly -- we had an enhanced communication initiative to increase the communication that -- opportunities for sponsors to get information from the review divisions and communicate with FDA. We've had over 350 of these kind of non-specific contacts outside of the context of a particular application, and we've established a team to handle these queries and questions. We have a team or an effort addressing meta analysis and the use of meta analysis. We posted a public meeting on meta analysis of clinical trials to support regulatory decision-making. For biomarkers and pharmacogenomics, we've had a public meeting to explore issues related to that, and we've had a first biomarker qualified and six letters of support issued so far. We have done a variety of staff trainings and learnings inside of FDA which

has been quite critical for the uptake and brining in of this new technology and new development programs consistently across the review divisions.

In terms of patient-reported outcomes, we've had a large public meeting at the beginning of April this year, public meeting to discuss clinical outcome assessments. The first PRO has been qualified. It's the exact tool during this last couple of years and we've issued guidance.

For rare diseases, we put together an internal team to help facilitate the development of drugs for rare diseases across review divisions. We've held public workshop and 17 novel orphan drugs have been approved just in the most recent year, calendar year 2014, so that's been quite successful.

We've issued a multi-year plan for our benefit-risk assessment framework and we've evolved that framework and refined it. It's now incorporated into the clinical review template and staff are being trained on its use in CDER and CBER's being used.

We've had 14 patient-focused drug development meetings to date. We're committing to do 20 such meetings. We have two more to go this year and actually, we've announced recently eight additional meetings that are going to be done in the next two fiscal years so that will put us over the total of 20 and we've learned a lot there that many of you have heard about in other meetings that we've had about that topic.

For REMS, we've had an expert workshop. We've drafted a report on how to standardize and evaluate REMS. With Sentinel, we've committed to explore the use of Sentinel for postmarket safety and so we've done a number of studies. At this point, we've initiated them to evaluate how much Sentinel can be used for specific safety signals and to what extent it could be used as a replacement for making a postmarket requirement to the study per the FDAAA with Title 9.

We have electronic submission standardizations. We've issued draft guidance to industry on the use of the electronic common

technical document. This is an effort to standardize and require standardization and standard electronic submissions from all industry parties. We have the ability to issue binding guidance in this area with an at least two-year timeframe for companies to be aware that that standard is going to be required so they can get ready an that's been very successful in terms of getting those submissions in electronically and that really enables us to do a more through efficient review because the applications are large, very large these days, over a million pages if you were to print it.

And we have a variety of efforts underway to standardize the clinical terminology, so we have about over two dozen therapeutic area standards being developed. This is to get the data related to clinical trials in the study data tabulation model, sort of C disk standard coming in, and so that data about trials is standardized and we're also able to examine that with review tools that make that much faster and more

efficient.

A little about the process, and I know this can't be read, but if you go get a copy of the statute, you can take a look at this. These are the provisions governing reauthorization process for PDUFA. A similar set is out there for, I think, the medical device user fee program but in particular, I want to draw your attention to these two. So we're having this public meeting today and as Dr. Ostroff said, this is really the beginning of the process. This is sort of our kickoff to the formal process to hold this meeting, have panels come and give us their views about the program. And so we're here to hear that today.

And the other thing to draw attention to for at least some of the stakeholders to be sure that we'll have this Federal Register notice that Terry mentioned coming out within the next week, and that's for the second process that I'm highlighting here, the periodic consultation. So according to the statute, not less frequently than

once a month during the negotiation process, we're going to hold discussions with representatives of patient and consumer advocacy groups to get their continued input on their -- what they think could be done to improve the process of the program and how we can improve the performance of the program. And so please be on the lookout for that because we're asking patient and consumer advocacy groups to identify whether you'd like to participate, and we'd like you to participate, if you want to, in a sustained way across all the series of meetings that we'll be having so that we can advance that discussion over that time. We've gotten tremendous benefit from your input last time and we hope to have another really rich process this coming time.

And here's just a few high-level priorities that FDA has identified for -- and these, no doubt, have offered no surprises but these are really the fundamentals. We want to continue to enhance the review program; continue to refine our ability to improve the quality and

the predictability of that process and the submissions that the companies send; enhance the financial soundness making sure it's a fair and efficient fee structure even as the types of applications that we get and things change over the course of the year since it was initially set up with all the funds we have coming in through this program and many other user fee programs that have been established more recently; ensuring that we have good financial management systems that are modern, that are able to give us good reporting and accounting of all these different streams of resources.

And finally, the purpose of these funds is to hire and retain the top talent. We have to compete with industry for that talent so we need very strong HR systems to be able to be as effective as possible to bring in the top talent to help us with this work.

With that, thank you very much and I'll turn it back to Terry.

MS. TOIGO: Thank you, Theresa.

(Applause.)

MS. TOIGO: And if the consumer panel can join me, Allan Coukell and Sally Greenberg.

MR. COUKELL: Good morning. My name is Allan Caukell and I direct health work at the Pew Charitable Trusts, and I'm pleased to be here today. Pew is a non-profit research and policy organization and we have a number of initiatives that touch on various aspects of FDA drug and medical device regulation.

My comments today focus mainly on the third discussion question of where should PDUFA VI go in the future. But for context, our perspective would be that the PDUFA program has been a success. Since its inception, review times have fallen steadily and the Agency has improved its scientific capacity to evaluate new medicines. Indeed FDA reviews drugs faster than its regulatory counterparts. Pew funded study from Yale University researchers which is consistent with others findings found that FDA's median new drug approval time was -- review time was 322 days

compared with 366 in Europe and 393 in Canada; 64 percent of drugs approved in both Europe and the U.S., for example, were approved in the U.S. first.

And has been mentioned today, FDA data show that first cycle review times have -- sorry -- first cycle successes have increased and that both manufacturers -- that suggests that both manufacturers and the FDA have clear understanding of the data needed to meet FDA standards.

What's more, drugs that are likely to represent important therapeutic advances are often approved even more quickly thanks to priority review and fast track and other mechanisms. All of this suggests that attempts to further shorten review times must eventually reach a point of diminishing returns. Certainly, now, the time to design and conduct clinical trials far exceeds FDA review time as a place to look for future efficiencies. And has been mentioned, PDUFA V started the process of using the user fee program to invest in the kind of regulatory science that

will help crack that problem or make progress there.

Perspective randomized trials remain the gold standard for the foreseeable future but all stakeholders would benefit from steps to speed the design and recruitment and execution of such trials. FDA is engaged in CTTI and efforts like the lung map trial which I'm sure will be spoken about in more detail today.

Other promising approaches like randomized registry trials have huge potential for certain applications to greatly reduce the time and cost of conducting trails, but developing such efforts takes time and resources. It takes dollars and it takes staff time, and those are resources that are unlikely to come in the form of additional appropriations from Congress, certainly not sufficient.

Many stakeholders have also been focused on the potential of observational data, real-world evidence as it's sometimes called, to address important clinical questions and the development

of electronic health records and claims databases and registries and so on has tremendous promise. And these sources of data also provide information typically not identified through clinical trials such as off label uses and specific real-world populations.

But the methodologies for conducting these types of studies are not fully developed, and FDA and stakeholders won't be able to fully utilize them until the methodologies exist. So, for example, FDA has spent on the order of $100 million dollars on the Sentinel -- mini-Sentinel program pulling together 18 data partners and something like 180 million covered lives yet there are still relatively few validated methods for asking questions in the Sentinel system. More work is needed to be done; and also, to make Sentinel into a public resource so that the industry and academic researchers can ask questions of this system.

And full disclosure: While I'm not representing the organization today, I sit on the

board of the Reagan Udall Foundation for the FDA which is undertaking some of that work to both develop additional methods for Sentinel and create a process for non-FDA stakeholders to ask questions.

But my point is a more general one which is that for FDA to work with manufacturers and researchers and clinicians to develop these methodologies, the Agency will need additional funding through the user fee program.

This approach, I think, also lends itself to another important trend which is targeted drug approvals, approvals for specific populations based either on a genomic profile or a clinical profile. But as we move into a world of targeted drug approvals, there will be a need for monitoring both how the drugs are used once they're on the market and for evaluating specific populations; again, that need to be able to look at a much broader expanse of data. And to do this, FDA will have to have sufficient scientific expertise to conduce reviews.

Pew, a couple of years ago, funded a study by the partnership for public service that found that FDA could improve its ability to hire and train and retain the physicians and scientists and other experts needed for the review of medical products. And certainly, the Agency faces increased demands on its workload from legislation and from scientific advances that will require increases in staff levels. To face these challenges, the FDA has been working to address its workforce challenges but certainly, as Theresa Mullin said, more remains to be done.

The bottom line, I think, is the FDA is known as the gold standard for ensuring the safety and quality of new medicines, but it's also a gold standard, I think, for facilitating drug innovation, and achieving further progress in this area will require an investment -- a continued investment in regulatory science and staffing and capacity from which all stakeholders, consumers, patients, the industry will benefit. Thank you.

MS. TOIGO: Thank you, Allan.

(Applause.)

MS. TOIGO: Next, we have Sally Greenberg from the National Consumers League.

MS. GREENBERG: Okay. Well, Allan was very timely so I don't want to get the hook from Terry, so I'll proceed with my comments.

So the National Consumers League wants to thank the FDA for the invitation to be here and I appreciate Theresa Mullin's very cogent review of the history of the PDUFA program.

The FDA and the National Consumers League actually have a shared history. We were begun in 1899 and if you read the exhibits up front, a lot of those efforts and campaigns to make sure that unsafe products were not exposed to consumers were efforts that the NCL undertook with the precursor agency to the FDA. So it's really great to be here and really be part of what FDA does every day to keep patients and consumers safe.

Today NCL provides government, business, and other organizations with consumer perspective

on numerous policy issues including child labor, privacy, food safety, medication safety, etcetera. From the first Pure Food and Drugs Act passed in 1906 which NCL was very much a part of drafting and advocating for to the more recent FDA Modernization Act, NCL has been working alongside the Agency to ensure the public is adequately represented and protected and that our medications are safe and effective.

Before I address the specific questions posed for this public meeting, I want to emphasize that our remarks are from the consumer perspective, and it's important to recognize the distinction between a consumer and a patient. Although definitions often overlap, we cannot appropriately address the needs of both without first understanding the distinction. First, consumers and patients may weigh risks associated with new drugs differently. On one hand, patients, especially those confronting a life-threatening illness, will likely place less emphasis on the risk associated with a new drug

than the average consumer.

Depending on health status, a consumer who is given accurate information about risks and benefits of a drug has the ability to weigh that risk-benefit calculus and to refrain from taking a certain drug or to choose a lower risk drug for a moderate to mild illness or condition.

A patient suffering from a serious illness is far more likely to take on greater risk to get the benefits from a specific treatment. This difference in risk assessment between patients and consumers is critical when considering the policy implications in this sixth reauthorization of PDUFA.

I'd now like to turn to the questions posed for this meeting. What's your assessment of the overall performance of PDUFA V thus far? NCL wants to be sure that in the quest to reduce barriers to new drug approvals, certainly a very important goal, the FDA, through the PDUFA program, doesn't lose sight of the importance of the Agency's mission of protecting and promoting

the health of patients and consumers. NCL strongly believes that patients and consumers deserve a drug approval process that provides timely access to safe and effective drugs while reducing exposure to harmful medications that pose undue risk.

NCL recognizes that PDUFA must balance the needs of consumers who are concerned about serious side effects with the concerns of patients who may be facing a life-threatening illness where time is of the essence. But even patients in great need may be harmed rather than helped by drugs that have been hastily approved without enough consideration of toxic side effects which can worsen the quality of life.

Thus, while it's important to have an efficient and timely approval process, there is still, in our view, too little emphasis on performance goals aimed at improving the safety and efficacy of drugs and too much emphasis on speed. For example, according to a 2012 United States GAO report on the FDA's performance goals

for new drug applications and biologics license applications, the FDA was able to meet most of its performance goals with the help of the funding authorized through PDUFA. At the time, funding authorized by the Act enabled the FDA to collect user fees totaling more than $529 million dollars.

More recently, according to FDA's Fiscal Year 2014 Report to Congress, as of September 30th, 2014, the FDA had completed over 1,400 view actions and met or exceeded the majority of its performance goals for Fiscal Year 2014.

The FDA meets performance goals by completing its review and issuing an action letter, approval, denial, or a complete response indicating the application is not ready for approval for a specified percentage of applications within a designated period of time. If this standard does not adequately address speed, applicants may choose to seek accelerated approval status which enables the FDA to grant approval on the basis of independent clinical trials. Moreover, this accelerated approval

status applies if the drug is intended to treat a serious or a life-threatening illness.

And another way the FDA speeds up its review of drug applications is by granting priority review. Although priority review applies only to drug applications with accelerated approval status, the FDA may grant priority review for applications that it expects, if approved, would provide significant therapeutic benefits compared to available drugs in the treatment and diagnosis or prevention of disease.

Performance goals are intended to protect patients from the risks of pharmaceuticals and not just to speed those drugs to market. We want to be sure that there are adequate safeguards in PDUFA VI. Currently, in our view, one of the most significant safeguards in the review process is the Agency's ability to deny approval or issue a complete response letter indicating that an application is simply not ready for approval.

Four years ago, the NCL expressed its concern to FDA that the public had too little

opportunity to fully engage in the PDUFA process. However, with the reauthorization of PDUFA V, opportunity for public engagement was made more readily available through patient-focused drug development initiative and benefit-risk assessment. Through this initiative, the FDA committed to conducted 20 public meetings, as has been referenced by previous speakers. And actually, NCL has had the chance to participate in several of these meetings and has been impressed with the level of public response; especially, it's so important to get patient and consumer perspective on these disease areas. So far the FDA, as has been noted, has held 14 meetings with plans for a few more this year and next year.

So we applaud the FDA for addressing those concerns that we highlighted and increasing public engagement, and we ask and urge the FDA to continue that engagement with both consumers and patients.

Question number two: What new features should FDA consider adding to the program? While

NCL commends the FDA for drug safety actions that have been implemented under PDUFA V, including enhancing benefit-risk assessment, we've suggestions for additional features.

I want to move to talk about our concerns about off-label prescribing. We've long urged the FDA to address some of the issues including off -- related to off-label prescribing and PDUFA VI presents an opportunity to do so. Off-label use is the utilization, as most people here know, of pharmaceutical drugs for unapproved indications, dosage, or forms of administration.

Our main concerns can be summed up with two points: ensuring that medications are used in safe and appropriate manners, and ensuring that consumers are informed that the medications being prescribed is approved for another condition and informed of the benefits and risks. We have reason to believe that many patients are unaware they're being prescribed off-label drugs when they are being prescribed those drugs.

A 2006 study analyzing prescribing

patterns for hundreds of commonly prescribed found high rates of off-label use with little or no scientific support. That same year, a Wall Street Journal poll found that about half of Americans thought that a medication could only be prescribed for a disease for which it has been approved demonstrating consumers' lack of understanding of the current regulatory scheme. These findings raise two important issues. Do consumers know that off-label prescribing exists and do they have any idea how common it is?

At NCL, we believe a consumer should be informed about the following if they are prescribed drugs off label: the availability of indicated alternatives, body of evidence supporting product use, special population considerations, approval status or use in other countries, and implications for insurance coverage.

As we have said in comments to the FDA over the last five years, we think funding should be directed to examining the safety of off-label

prescribing in PDUFA VI to address consumers' lack of awareness and understanding of the practice. Particularly, we suggest tracking the use of off-label medications by the public would contribute to our understanding of the use and health and safety implications of off-label prescribing.

The second issue we want to address is the direct to consumer advertising. We're a little bit of a broken record on this issue but with over $4.5 billion dollars spent on direct to consumer advertising and over 91 percent of Americans reporting that they have seen or heard advertisement for prescription drugs, DTC advertising has become an integral part of communicating information on prescription drugs.

A 2013 content analysis of false and misleading TV ads found 33 percent of prescription and non-prescription drug ads were objectively true; 57 percent were potentially misleading; and 10 percent were false. So consumers are continually exposed to these ads.

We think it's imperative that the FDA

have the staff and resources to ensure the ads are accurate and not misleading before they reach the public. We strongly believe the FDA should seek the authority to require that all DTC ads undergo review before public dissemination. This would enable Agency staff to work with the industry to revise materials and content where needed so that misleading information does not reach consumers. Without the authority to review a condition of broadcasting, product sponsors have no incentive to submit their ads for Agency review.

So we urge the FDA to make the review of ads for newly approved drugs a priority, and we believe there should be a moratorium -- consider -- the FDA should consider a moratorium in all DTC advertising for new drugs, especially those deemed to have inadequate safety information. Based on available safety data, the Agency could be given latitude in determining the appropriate length of the moratorium on a product-by-product basis.

And we'd like to suggest that user fees be allocated to support hiring of additional staff

to review ads and respond to industry feedback in a timely fashion. We think there is a current dangerous imbalance between the volume of DTC advertising and the resources available for monitoring and reviewing the advertisement and this imbalance becomes greater with the growth of internet and social media advertising for prescription drugs. Thus, it will be more important than ever for FDA to have the resources to ensure that consumers receive balanced information, because so much of what consumers know and understand about drugs comes from what they see on television and in other media sources.

So in conclusion, although we convene here today as stakeholders, we are all both patients and consumers at different times in our lives. We rely on this incredibly important Agency, the FDA, and the pharmaceutical industry to work thoughtfully and carefully in approving new drugs for the public. As advocates, NCL will continue to work collaboratively with all of you and with other non-profit organizations and

industry stakeholders to ensure that consumers and patients have access to the safe and effective drugs and treatments they need and hope to have from the work of this very, very critical regulatory agency. Thank you very much.

MS. TOIGO: Thank you, Sally.

(Applause.)

MS. TOIGO: So if the patient panel can make their way to the front and just a reminder that these are listening sessions for FDA. There are FDA staff that are involved in the negotiation process that are sitting in the audience. The time for further discussion on any points that were raised by our presenters will be during the public meeting discussions that Theresa referred to that we'll see in the Federal Register notice.

Okay. We'll start with Paul Melmeyer from the National Organization of Rare Diseases.

MR. MELMEYER: Well, thank you very much and NORD would like to thank the FDA for allowing us to present here today and provide our views on the Prescription Drug User Free program.

So before getting into our goals for PDUFA VI, I'd first like to provide a bit of an introduction to NORD and to rare diseases. So just a few facts about rare diseases. There are an estimated 7,000 known rare diseases; 1 in 10 Americans has a rare disease, so that is 30 million Americans in the aggregate. And a rare disease is defined as a disease that affects 200,000 people or fewer within the United States in any given year. Two-thirds of people with rare diseases are children and 80 percent of rare diseases have a genetic component. While there are 7,000 known rare diseases, there are only approximately 450 orphan therapies treating about 350 diseases so, obviously, there is much more work yet to be done.

While rare diseases are -- you know, run the gamut and the -- in symptoms as experiences for rare disease patients, there are common experiences for the rare disease population. First and foremost, it takes years to obtain a diagnosis. I believe the average for time to

diagnosis for a rare disease patient is approximately seven years. And, of course, there are many undiagnosed patients who are still looking for a diagnosis that have been searching for years.

There are very limited treatment options and due to the small populations of rare disease patients, rare disease therapies, orphan therapies are naturally more expensive and this, of course, can create reimbursement problems within private insurance, Medicare, Medicaid, and other payers.

So a little bit about NORD's history. We were founded in 1983 following the passage of the Orphan Drug Act by the very same patient advocates who were very involved within the passage of the Orphan Drug Act. And since then, we have been engaged in providing policy and regulatory advocacy for the rare disease population. We provide education programs for patients, professionals, medical students, researchers, essentially anyone who's a stakeholder within the rare disease community. We

also provide patient assistance programs to rare disease patient population. We hold patient networking meetings to bring the rare disease patient population together to meet others with the same or similar disease. We are a member organization. We have over 230 individual patient organizations who are our members. They represent single diseases or single disease families and we provide them with regulatory and policy advocacy as well as the various other initiatives we have listed here.

So getting into our goals for PDUFA VI, first and foremost, we must ensure that the user fee agreement does fund the FDA appropriately. While we will not be getting into the detailed discussions on exactly what the user fee amount should be, and I think we're more than happy to stay out of those detailed discussions, we do want to ensure that the user fees do then match up appropriately with the appropriations to ensure that together these total funds will fund the FDA appropriately to ensure safe and expedient review

of drugs and biologics.

We are very proud to be founding members of the Alliance for a Stronger FDA and through the Alliance, we have successfully advocated for increased funding for the FDA through Congress and we look forward continuing to do so.

Our second priority is to strengthen and incorporate the patient voice throughout the drug development process. I think this starts with patient-focused drug development. We were very supportive of the passage of the patient-focused drug development piece within the 2012 FDASIA bill and we have been very pleased with the program since. We've been at or I personally have been at most, if not all, of the patient-focused drug development meetings for patients with rare diseases. And I do know that the patients have come aware very pleased with the meetings and that they have been very happen to participate within the meetings.

However, we do need to define the next step within patient-focused drug development.

While it's great to have the 20 authorized required meetings, and as Theresa was saying earlier, I guess it will be upwards of 22 or 23 in total by the time 2017 comes to a close, we need to also ensure that patients that do not fall within the 22 or 23 disease states that will have meetings are still represented within the patient-focused drug development initiative. So whether that be holding their own patient-focused drug development meetings outside of the FDA, with the FDA's participation, or through a guidance process such as the Duchenne's community just completed. That's the rare disease patient population who has not already had the chance to participate within patient- focused drug development still has that chance.

We also want to ensure that rare disease patients have the opportunity to sit on advisory committees, and I think the FDA is gone a very long way to ensuring patient participation within advisory committees. We're very pleased that there is a patient on every single advisory

committee if they can be found, of course, and that they are a voting member.

However, we still have various -- we're still seeing various issues on conflict of interest out in the marketplace and that various rare disease patients as well as physicians and researchers are found to be conflicted, and this is a particular problem within the rare disease community since there are so few experts in any single rare disease. So if there is some kind of conflict of interest found within maybe just one or two researchers or physicians, that then there won't be any expert within the advisory committee whatsoever. And, of course, the rare disease community is a very small community, especially within diseases that maybe only have 30 or 35 patients, which is actually the majority of rare diseases. And oftentimes, of course, any expert who might be the only expert in the United States is going to be working with the entire rare disease community which then might lead the FDA to determine them as conflicted.

We also want to ensure greater coordination across centers on patient involvement. We believe there are great initiatives going on within each center on patient involvement but there doesn't seem to be much coordination across the centers on ensuring patient voice is incorporated within the drug, biologic, and device review process.

And then finally, we also want to ensure that patient voice is included throughout the development process, not just within the end-stage review of the drug. And I think many of the patient involvement initiatives or proposals have focused on the end of the review in that the patients' benefit- risk is incorporated as well as the patient voice might be incorporated within the advisory committee. And I think within the actual legislation where we're currently looking at within -- that has just passed at House and it's now going over to Senate within 21st Century cures, we are supportive of that legislation and we are supportive of the patient-focused drug

development piece within, but again, it just focuses on the very end-stage, the review of the drug rather than the entire development of the drug.

A third goal we have for the PDUFA discussions is to ensure orphan incentives remain strong. And I want to mention two programs that were included within the FDASIA Bill. That would be Section 908 which is the rare pediatric disease priority review voucher program. This program would provide a priority review voucher to a company that's first developed a drug for a rare pediatric disease. This program was initially passed as a pilot, meaning that only three vouchers can be awarded and then once that third voucher is awarded, there's a one-year timeline for the GAO to develop a GAO report on the program and then the program would expire if not reauthorized. So while there is a reauthorization within the 21st Century Cures' language, of course, there are many hurdles still to be passed with 21st Century Cures. And if that rare disease

pediatric -- rare pediatric disease priority review voucher program is not reauthorized, would like to renew those discussions within PDUFA VI discussions.

And then finally, would also like to see the Orphan Products Grant program strengthened and expanded. There was funding in Section 906 of FDASIA included for this program, but that funding was only for 2013 through 2017, so we want to ensure that that program, which is incredibly valuable for orphan development, is continued. That program has -- can credit 45 orphan therapies that have come to market have gone through that program, and we believe that it is one of the strongest programs within the FDA for encouraging orphan product development.

Fourth, we also want to ensure that rare disease patients have access to off-label therapies. Of course, the vast majority of rare disease patients are treated off-label since only 350 diseases that rare diseases have an on-label therapy. And so we want to ensure that therapies

that do not have the indication on the label for that rare disease yet can treat that rare disease are able to reach that rare disease population.

And then finally, we also want to ensure that there is consistency across review divisions in the use of expedited review pathways. Of course, rare disease patients and rare disease therapies oftentimes benefit from the existence of expedited review pathways. And so while there have been review divisions who have been quite good in appropriately using these expedited review pathways, we want to ensure that the expedited review pathways are used throughout the FDA in each review division consistently.

So again, thank you for inviting me to speak today and thank you again.

(Applause.)

MS. TOIGO: Thank you, Paul. Next, we'll hear from Marc Boutin from the National Health Council.

MR. BOUTIN: Well, first, let me thank FDA for the invitation to participate and let me

welcome everyone here today. Good morning, everyone. You have a really low energy. Let's try and build up the energy in the room a little bit. Good morning, everyone.

(Chorus of good mornings.)

MR. BOUTIN: Much better, thank you. I want to get a sense of the audience. How many people are here from the FDA?

(Whereupon, a showing of almost halve the audience are from the FDA.)

MR. BOUTIN: So quite a few folks from the FDA. How many people are here from business and industry?

(Whereupon, a showing of almost half the audience are from business and industry.)

MR. BOUTIN: Good percentage. How many people are reporters? A few, not too many raising their hand; we have a few. How many are here from the patient advocacy community? Good. We have a good group of people here. I appreciate that.

I'm here from the National Health

Council and the National Health Council is an umbrella organization of patient advocacy organizations. We were created in 1920. We provide a united voice for people with chronic disease and disabilities. Our core membership are the leading patient advocacy organizations in the United States, groups you would know like the American Cancer Society, American Heart Association as well as groups representing rare and less known diseases. We also have other membership categories including the provider community, the family care-giving community as well as business and industry, but the governance is controlled by the CEOs of the patient groups.

And we focus in on two things. One, we want to ensure that all people have access to medical care that meets their needs; and two, we focus in on ensuring that innovation occurs so that the many people without effective treatments get the treatments that they need. Now a quote that has been thrown out there multiple times, there are between 7,000 and 9,000 diseases of

which we have effective treatment for about 500. We have a lot of work that needs to be done and the patient community is committed to ensuring that we develop safe and effect treatments.

I want to leave you today with two messages and the first message is that your participation is critical. We in the patient community created the energy that was the catalyst for the very first PDUFA agreement. It was the HIV/AIDS movement that was saying, "We need access to treatments." They were chaining themselves to the fence. They were protesting. They were coming to the FDA saying, "I want access to experimental drugs," and the FDA appropriately said, "We don't know if they're safe and effective." But that community said, you know what, I'm going to be dead in six months, let me try. We need to figure this out. That created the basis for early access compassionate use program. It was that community that said we are taking too long, there's a drug lag, we need to do something.

The first PDUFA agreement was enacted and you saw a great reduction in that lag. And with the second PDUFA, you saw review times start to get shorter. And it was at that point in time that the patient advocacy community stepped back from the process. And we saw great advances in the HIV/AIDS arena. We saw great advances in the oncology space. But for many of the other conditions, we were not seeing the same level of advances. And in fact, it was at this point in time you saw a dramatic shift to the consumer perspective. And I'm here to say that the patient community and the consumer community are part of the same group of people. We are the same stakeholders. But a consumer perspective and a patient perspective are on opposite ends of the spectrum, and I applaud Sally for addressing that distinction in her comments.

For people with chronic conditions, they're people that will have their disease until they die. They will go in and out of the healthcare system to manage their lives, to manage

the quality of their lives but ultimately, they will likely die as a result of their condition or issues related to that condition.

Consumers are people that go in and out of the healthcare system as needed. They are skiing and break a leg or they have an infection. They're perspectives are very, very different and even within a disease state, as you see the development of treatments flourish, the perspectives shift. If you look at a condition like ALS, there is a strong sense of urgency to have some effective treatment. And for many with ALS, they would be willing to take substantial risk to get the opportunity to have another year or quality life.

But if you look at conditions with multiple effective treatments like heart disease, the perspective starts to shift more to a consumer perspective because there are effective treatments. If you look even within a specific condition without effective treatments and look at where you are in the sage of the progression of

disease, like Parkinson's, somebody newly diagnosed may be less likely to take a risk on a treatment that might prolong their lives but somebody at the end-stage of Parkinson's who's having a hard time having a relationship with their family, having a hard time communicating, having a hard time sleeping might be much more willing to take a substantial risk. The perspectives shift depending on where you are on that continuum of the spectrum and your own personal goals and aspirations. It's critically important that we understand that point.

And it was during the PDUFA IV negotiations that many of us in the patient community started to re-engage because the focus became all about safety and while there is no patient advocacy organization that does not support safety, we are equally concerned about getting good effective medicines into the hands of people who are suffering under the burden of their disease or do not have particularly effective treatment currently. It was in that agreement

that we saw a huge push towards safety and we felt we needed to have more input into the process.

And one of the great things that happened in PDUFA IV was that there was a push to have these stakeholder meetings and that allowed us to engage in PDUFA V in a very, very different way. Many of the patient advocacy groups in the room met on a regular basis with the FDA. We had the opportunity to say what was important to us, what we wanted to see in that agreement. And one of the things I learned through that process was that the things that were important to us in the patient advocacy community were often on page three or four of other people in particular or in addition to the negotiators from the biopharmaceutical sector and the FDA. They were primarily focused on getting the agreement done, understanding what the mechanisms would be, how the review process would work, and how the cost would be delegated, all of which was critically important and nothing that we didn't care about but it was not our priorities.

Our priorities were we wanted to see a radical change in how benefit-risk was communicated to the general public so that we could see how that judgment was being made. And it was at that point in time the patient community said loud and clear this is not a scientific decision. There may be scientific inputs into the determination of benefit and risk when FDA makes an approval, but at the end of the day, benefits and risks is a judgment and it has to reflect the perspectives of the end user.

And up until the last PDUFA agreement, we had very little way to understand how FDA was making that judgment so we called for a framework and FDA has been piloting that. We called for more resources for patient-reported outcomes and biomarkers. We called for more resources for rare disease. We also called for the 20 meetings to be held at the FDA. We were incredibly appreciative of the process of going through the FDA discussions as a stakeholder group but we wanted additional input. All of that came to bear in

PDUFA V. We're now in the midst of implementing it and I would say it is going incredibly well with an all-time high in terms drug approvals. We have incredibly sophisticated groundbreaking treatments coming forward. We have the FDA, for the first time, meeting with large groups of patients and their advocates to really understand the burden of disease, to understand the impact on their lives, to understand what was important to them. And in every meeting, people have walked away saying what I thought was most important to this patient population wasn't what was most important; it was something else. What an incredible "ah-ha" moment for all of us to have. All of that information needs to be brought into the regulatory process, but it also needs to be brought into the continuum of drug development.

Now I've asked this question before but how many people in the room have an Apple phone? Raise your hand.

(Whereupon, most audience members indicate in the positive to having an

Apple phone.)

MR. BOUTIN: Okay, most of you. How many of you have Samsungs?

(Whereupon, a showing of approximately 30 percent of the audience indicate in the affirmative positive to having Samsungs.)

MR. BOUTIN: A few of you. I'd like to say you guys are the innovators. How many of you have Blackberrys?

(Whereupon, a showing of approximately 10 percent indicate in the affirmative to having a Blackberry.)

MR. BOUTIN: Here's where you see everybody from the FDA.

(Laughter.)

MR. BOUTIN: In fairness to the FDA, I understand that they are much more secure. Having said that, there is not a single company that develops these products that would even change the color on the outside of the casing without doing extensive research to understand the perspective

of the end user.

And I'm going to wrap it up with my last point and that is this -- thank you, Terry -- we have to do a better job of incorporating that perspective into drug development. We need to remove the barriers that prevent companies from engaging with patients at the front end, needs to be done appropriately. We need to be able to take that data and bring it into the regulatory approval process. And it's more than just meeting with one individual patient. There is a science that has been built up over the course of 60 years on how to do this. We use it in the social sector. We use it in politics. We have a President that's been elected twice using these methods. We can understand at a granular level what is important to patient populations, segments of patient populations, and we can take that data, make much higher value products, get it into the label so it can be part of the discussion between a doctor and a patient, and they can make an informed decision about the treatment that they

want to take for them. That's where we need to go in PDUFA VI.

I thank you for your time and I encourage you to participate in the process. Thank you.

(Applause.)

MS. TOIGO: Thank you, Marc. Okay. Next, we'll hear from Jeff Allen from the Friends of Cancer Research.

MR. ALLEN: Hi, good morning. Thank you for the invitation to join in the kickoff of this important process. My name is Jeff Allen. I'm the Executive Director of a group called Friends of Cancer Research which is a think tank and advocacy organization focused on accelerating the pace of developing safe and effective new medicines.

In general, the value of the PDUFA program, since its enactment, is obvious by the numbers. In 1993, the median time for approval was 19 months for a new molecular entity. Today the median approval time for an NME is 10 months.

In 1993, 10 percent of drugs were approved first in the U.S. Today over 60 percent of drugs are approved first in the U.S. In oncology, which I am most familiar with, over the last decade, all of the drugs approved in the U.S. and Europe were available to U.S. patients first. This is largely due to the goals and the resources that have been provided through the PDUFA process.

So it's clear that the PDUFA program has accelerated the time in which new drug applications are reviewed and subsequently enhanced access to new medicine that demonstrates a favorable benefit risk profile. The 2012 PDUFA V agreement sought to continue this trend through several important programs that made adjustments to the development and review processes for new drugs, a couple of which I'd like to provide a few comments on today, the first of which is the new molecular entity review program that was described by Dr. Mullin in her opening remarks.

The program was developed in order to try and increase the rate of first cycle approvals

which prior to PDUFA V was around 55 percent. The recent interim analysis of the program showed that the enhancements to the program have thus far increased the cycle of application approval rates to nearly 72 percent and even higher for those that were designated as priority review. This demonstrates the effectiveness of the program to reduce instances for which the review clock resets. One element that was implemented in order to enhance first cycle approval was a 60-day waiting period before the review clock starts. While this has helped to accomplish the goal of improving first cycle reviews, there are instances where it hasn't been necessary for several of the successfully approved NMEs in oncology which haven't needed the extra two months.

I'm not advocating that these two months haven't provided substantial benefit in terms of reducing the -- or increasing the number of first cycle approvals but as part of the re-examination process of the program, it may be useful to examine any identifiable best practices that were

able to be applied in instances for which the 60-day waiting period may not be needed.

The second area is the patient-focused drug development program. In just a couple of short years, the patient-focused drug development program has created an important venue for patients and advocates to share their experiences with specific diseases. This has helped to expand the baseline knowledge about different diseases and their current treatment options to add to the information that may be contained in a future new drug application.

As the patient-focused drug development program is re-evaluated in the context of the next user fee negotiation process, we hope to see this program continue and further operationalized. This could include development in methodological considerations for areas such as the collection of patient experience data outside of the development process, quantifying benefit-risk balances for different diseases and for incorporating patient-report outcome tools for different context abuse

within drug development.

In addition, tools for communicating with patients should be examined as well. This could include assessing how product labeling could be enhanced to improve patient use and understanding as well as how external information about drugs such as exploring how information hubs such as clinicaltrials.gov could be an improved tool for patient-oriented information.

Finally, as part of the total legislative package included in PDUFA V, the breakthrough therapy designation was created. While this is policy, as Terry mentioned, which is not necessarily the focus of today, it certainly has impacted process. I'd like to take just a moment to share some preliminary information about the breakthrough designation program thus far. As of last month, the FDA had received over 300 requests and granted 93 designations, and 24 of those indications have been approved; 36 percent of those designations have been in oncology demonstrating that designation is being applied

widely when new drugs for an unmet need are showing unprecedented clinical activity early in development. The designation instigates an intense collaborative process between the FDA and the sponsor to design plans to expedite the development program or the drug.

While it's difficult to measure the differences between a drug with the designation and without due to the diversity of the diseases being treated, we have tried to look at this a little bit to understand what the results of designation provided. When we looked at oncology drugs that received the breakthrough designation versus those that didn't over the same period of time, we found that the review times of the breakthrough drugs was an average of 100 days shorter and the development times from IND submission to NDA submission averaged 7.8 years for non-breakthrough drugs and 6.6 years for a breakthrough designated drug. This shows that for these potentially transformative drugs, the collaborative strategies are successful in

accelerating the development without compromising standards.

While the breakthrough designation has created positive enhancement, it's also helped raise the awareness of important challenges that still exist across all of drug development. Perhaps these are areas that could be considered further in terms of the user fee reauthorizations. These could include enhancing the interactions between centers to further align administrative processes for drugs that are developed with a companion diagnostic. In terms of breakthrough designations, over a third of the drugs designated contain a pharmacogenetic marker associated with their use, so this is becoming increasingly important.

Second, the need for developing new technologies for advanced manufacturing processes, CMC, and drug quality assessments is becoming equally as important as demonstrating clinical benefit in terms of expediting new drugs.

And finally, there may be opportunities

for developing methodologies and strategies for appropriate use of real-world evidence, particularly as part of postmarketing study commitments.

So thanks again for the invitation to be here. I look forward to engaging throughout this long yet important process.

(Applause.)

MS. TOIGO: (Inaudible.)

MS. BENS: Good morning, everyone. My name is Cynthia Bens and I'm Vice President of Public Policy with the Alliance for Aging Research. And I'll just put a warning up front, public policy is in my title so I'm sure I will stray into that area.

I'd really like to thank FDA for inviting me to be here today and for those of you who aren't familiar with the Alliance for Aging Research, we're a patient advocacy organization that's based in Washington, DC. We were founded in 1986 and since then, our mission has been to promote research into aging and its application to

improve the experience of aging and health. In the early days of the Alliance, our primary focus was on supporting aging research at the National Institutes of Health and it was about 10 years ago that we started focusing on FDA regulatory issues and their impact on translation.

Most of us are keenly aware that our population is aging at an unprecedented rate. Ten thousand baby boomers are turning 65 every day and that's up from 6,000 just four years ago. People age 80 and older make up the fastest growing segment of our population, and right now 10 percent of the U.S.

population is 80 or older, and that's going to triple by the middle of this century.

It's our view that the need for innovative treatments that respond to the declines people face with age have never been greater. The good news is that many people are living healthier lives as they age, but the truth is that most older adults still face significant periods of illness and disability later in life. They

experience forms of cardiovascular disease, cancer, diabetes, bone and joint degeneration, muscle wasting, vision and hearing loss, neurological diseases, persistent pain, and incontinence.

We believe that we're only going to realize the benefits of new therapies if FDA h as access to the resources necessary to evaluate them. The industry is certain that their products are going to be evaluated in a timely manner and that we're all working together to serve the best interests of patients.

Recognizing the critical role that FDA plays in shaping medical product development, the Alliance began a coalition of more than 50 non-profit groups in 2005 called "Accelerate Cures and Treatments for Alzheimer's Disease," or as we call it, ACTAD. It's through this coalition that we can lead patients, patient advocacy organizations, leading researchers, and industry scientists to engage directly with the senior leadership at FDA and representatives from the neurologic product

division to tackle overarching challenges with Alzheimer's drug development.

ACTAD has been incredibly successful establishing close connections with the review division and facilitating exchanges on topics such as clinically meaningful benefit for Alzheimer's patients, issues with designing phase two clinical trials for Alzheimer's disease that result in success in phase three and the potential for combination therapy in Alzheimer's disease. And I credit FDA because that was actually their idea.

Our advocacy has contributed to FDA making a number of positive changes. These include the creation of the patient caregiver representative program for Alzheimer's disease, a working group called "neurology across FDA" which actually does align activities on Alzheimer's across centers, and a draft disease-specific guidance on Alzheimer's disease.

And acknowledging that in addition to Alzheimer's disease, physical disability is another leading cause of institutionalization

among older adults, the Alliance started the Aging in Motion Coalition in 2010. AIM is trying to clear a regulatory pathway for significant muscle wasting in older adults and this is called sarcopenia. Sarcopenia is currently not recognized as a condition so we're actually tackling issues related to drug development for this condition on a number of fronts, and this includes being one of the first patient advocacy organizations to work with FDA to pursue qualification of a functional endpoint for use in clinical trials.

We continue to engage in the PDUFA reauthorization process because we understand that user fees play an essential role in maintaining an FDA review process that efficiently delivers safe and effective treatments for patients who need them. I had the pleasure of representing the Alliance throughout the entire patient consumer consultation process leading up to the fifth reauthorization of PDUFA and had the great pleasure of getting to know Theresa and Patrick and everyone sitting in the first two rows.

And it was after such a positive experience with ACTAD and AIM that we became fierce supporters of the patient-focused drug development imitative during PDUFA V. Like many of the patient advocacy groups here today, it was no surprise to us that FDA was receptive to the idea of holding patient-focused drug development meetings. And a priority of ours in PDUFA 6 is going to be to pursue funding for the continuation of FDA-led patient-focused drug development meetings. We believe these meetings are valuable for several reasons.

First, they provide unfiltered testimony of patients for medical reviewers evaluating treatment for diseases they may not actually have a firsthand experience with. Second, the PFDD meetings have largely been targeted at diseases where FDA themselves have identified knowledge gaps. And lastly, they allow FDA to have a chance to learn about diseases and conditions they'd like to better understand, and this is especially true for sarcopenia which I'm pleased to announce has

been selected as one of the eight conditions that was granted a PFDD meeting in FY 2016 or FY 2017.

We've observed that the PFDD meetings have led to a cultural shift across FDA elevating the way in which regulators view the value of patient input. We're thankful that this is being embraced by other stakeholders including industry.

We understand that there is the desire for some patient-focused drug development activities to shift in the public-private partnerships and we'd offer a word of caution. As an organization leading two effective coalitions in the regulatory space, we've learned that there is no one-size fits all solution to gathering and employing patient input effectively across the drug development process. For both our Alzheimer's and sarcopenia activities, our methods for trying to advance therapeutic development have had to be very different. And we think that FDA is headed in the right direction with PFDD and we feel their best positioned to continue to lead this initiative independently.

In PDUFA V, the Alliance also prioritized enhancements at FDA aimed at furthering the use of patient-reported outcome measures in clinical trials. We were pleased that FDA held a public meting on PROs and other drug development tools to clarify the ways in which stakeholders can pursue their development. FDA released a guidance broadly outlining the principles of PROs in 2009 and how they might be incorporated into labeling. Despite the recent public meeting and guidance, challenges remain in utilizing PROs for diseases like Alzheimer's.

We would encourage the dedication of resources in PDUFA VI to support additional workshops aimed at the feasibility and reliability of incorporating PROs in trials for complex diseases. Going through the qualification process for drug development tools where there's no existing guidance like we're doing with the Aging in Motion coalition presents obstacles of its own. For this reason, we would support the addition of fees in PDUFA VI to allow for new guidance on

performance outcome measures, observer reported outcome measures, and clinician reported outcome measures.

We're pleased with the emphasis in PDUFA V on expanding the availability of data on age, sex, and ethnicity, CDER's public process for developing an action plan on sub populations, and placing snapshots of data that is available from clinical trials on FDA's website is a positive first step in uncovering where data gaps exist that must be filled so that we can better understand how people respond to treatment. We'd like to see this work continue and be expanded.

The European Medicines Agency adopted a geriatric medicine strategy in 2010 that encompassed activities related to the incorporation of elderly people in clinical studies, ensuring appropriate representation of older adults in clinical studies, considerations for comorbid conditions, and the development and use of age-specific endpoints. Support for this increased representation of older adults in

clinical trials already exists at FDA. I've heard it. I've seen it. And we know that there are many things that actually are trying to achieve these types of activities and so we'd encourage FDA to pursue a coordinated strategy related to the geriatric population.

There is great interest in FDA promoting the use of evidence from observational studies or registries to support the approval and use of new drugs or to satisfy post approval studies, and Allan mentioned that in his comments earlier today. And this interest was very evident in the Capitol Hill debater on 21st Century Cures. We see great potential future use for a well-designed real-world evidence program in many diseases, but we agree with Allan that we don't feel that there is widespread agreement on the best methods for collecting real-world evidence for the use in supporting regulatory decisions.

We would encourage FDA to start a pilot program on this that lays the foundation for future guidance on the application of real-world

data in approval decisions and PDUFA VI fees would be an important step launch this program.

Finally, I'd like to recognize the resounding success of the breakthrough therapy designation across a number of different diseases and we all have Jeff Allen and Allan Coukell at the Forensic Cancer Research to thank for that. While the support -- we support the continuation of this pathway, we remain concerned about FDA's ability to conduct the number of high -- the high number of breakthrough reviews and meet timelines for reviewing other types of drug applications without any more dedicated resources. We believe it's worth considering the addition of funds in PDUFA VI to support the breakthrough therapy pathway.

Like many of the representatives on the panel today, the Alliance for Aging Research advocates for overall funding of FDA with a strong emphasis on finding the right balance between user fees and appropriated funding. We like to believe that our asks in PDUFA VI are modest and are

really intended to reduce the time it takes to bring safe and effective treatment to the U.S. market. So all of us here know that that's actually the primary purpose of the PDUFA program.

So I'll just close by saying that we've been pleased with the progress FDA has made under PDUFA V, and we know that this is just the start of a year-long process so we look forward to joining with other stakeholder =s n providing ongoing input as the PDUFA reauthorization moves forward. Thank you all for your attention and thanks again FDA for inviting me here.

(Applause.)

MS. TOIGO: Thank you, Cynthia. And our last speaker on this panel is Maureen Japha from the Milken Institute and FasterCures.

MS. JAPHA: Thank you. Good morning. My name is Maureen Japha and I am legal counsel for the Milken Institute and a member of the policy team at FasterCures. I'd like to thank FDA for giving us the opportunity to participate here today in this important initiative.

For those of you who may not be familiar with our organization, FasterCures is a non-profit, non-partisan DC-based center of the Milken Institute. We work to bring greater efficiency to the biomedical research process across diseases and look to find ways to reduce the time it takes to move promising discoveries from lab to patients. Our mission is to save lives by speeding up and improving the medical research system. To that end, we work with all sectors of the medical research and development ecosystem, from patients to academia to industry and government.

Prior to joining FasterCures, I worked for a law firm where we regulatory advised clients on how to navigate the regulatory landscape at FDA. In my new role at FasterCures, I have the exciting opportunity to work with our colleagues in industry, academia, and government to explore how the landscape can be improved and to identify ways to implement those changes in a productive way.

An area of increased focus for FasterCures and many patient advocacy organizations, many of whom have touched on this already today, centers around enhancing the science of patient input to more effectively incorporate the patient voice into all aspects of the drug development process. It's important to understand that efforts to enhance the science of patient input should not be viewed as a feel good exercise to simply give patients an honorary voice in the process. Incorporating patient perspectives into regulatory decision-making has real utility for all stakeholders.

This utility was highlighted for me as I reviewed materials from a recent meeting of FDA's Oncology Drugs Advisory Committee where the advisors were asked to discuss, not simply vote "yes" or "no," on the key questions of whether study data supported a positive benefit-risk assessment for an experimental therapy to treat squamous non-small cell lung cancer. This deadly condition has seen no new treatments in over 15

years. As advisory committee members wrestled with data that showed a statistically significant yet arguably small improvement in overall survival, it was striking to me how much this discussion could be enhanced with data showing the effected patient community's range of minimum expected benefit and maximum threshold for harm. Such information can inform the dialogue and ultimately the regulator's decision as to whether to approve this therapy.

Traditionally, opportunities for patients to inform regulatory decisions regarding medical products have been limited to participation by single individuals who may not represent the range of perspectives and expectations of the broader patient population. PDUFA V started to shift this traditional paradigm in significant and important ways by establishing new approaches to more effectively integrate patient perspectives into the regulatory process as discussed by my colleagues here today.

Specifically, FDASIA, the authorizing

legislation for PDUFA, included a directive for FDA to establish a structured benefit-risk framework to improve the transparency and clarity of FDA'S benefit- risk decisions. In 2013, FDA released a proposed five-year implementation plan and has begun piloting that structured benefit-risk framework. In addition , as part of PDUFA V, FDA committed to host at least 20 patient-focused drug development meetings. And as discussed here today, these meetings have been a huge way and an important opportunity for patients to really present their voice to stakeholders on a specific disease and condition and give FDA reviewers a better understanding of the patient experience of the disease and available treatment options.

The introduction of the structured benefit- risk assessment framework and the launch of the PFDD initiative have been huge catalysts for change, and I want to commend CDER and FDA for the advancements achieved under PDUFA V. These efforts sent a signal to the entire ecosystem that FDA was willing and ready to explore a more

patient-centered drug development and have helped advance the discussion significantly.

Today, as we look toward the reauthorization of PDUFA VI, we have the opportunity to improve upon these advancements and integrate patient input into regulatory decision-making even more effectively.

I want to highlight three actions that, if implemented, we at FasterCures believe can meaningfully advance the way patient input is integrated into drug development. First, patient perspectives should be integrated throughout the drug development pipeline, not just at the time of approval as contemplated by the current benefit-risk framework. Although the public hasn't yet had an opportunity to see FDA's use of the benefit-risk assessment framework in connection with a drug approval, our understanding is that it will be used primarily as a communications tool. This framework has the potential to be much more and could have real value as a tool to guide decision-making throughout the drug development process.

Patients would benefit from mechanisms that allow regulators and sponsors to explore and address patient perspectives earlier in the pipeline.

Second, transparency is essential to advancing the science of patient input. For approved drugs, FDA should clearly explain how patient perspective data guided its regulatory decisions. For drugs that are not approved, it is important for stakeholders to understand how the benefit risk framework influenced decision-making. Recognizing that sponsors have legitimate concerns about maintaining confidentiality, a compromise approach would be to release appropriately redacted versions of the structured benefit risk assessment as part of the advisory committee process or after a complete response letter has issued.

Third, we need to work together to develop appropriate scalable and sustainable analytical methods and practices that will more effectively integrate patient perspectives into all aspects of drug development and delivery from

preclinical through phase three trials and beyond. The PFDD meetings have been an important and critical step forward but there are some limitations. Specifically, we need to explore how the information -- we need to better understand how the information generated from these meetings will inform regulatory decisions and how patient perspectives regarding diseases or conditions that are not the subject of a PFDD meeting can be meaningfully collected and submitted to FDA.

Patients, companies, academics, and regulators are poised to co-develop appropriate methods and practices and guidance and direction from FDA about its evidence requirements will accelerate and enhance this process.

In addition to improving the use and implementation of the benefit-risk framework, PDUFA VI also presents an opportunity to revisit the procedure for validating patient-reported outcomes or PROs. As discussed earlier, at present, only one PRO instrument has been qualified by FDA. However, FDA's efforts to

develop a compendium of clinical outcomes assessment is a commendable and important step toward bringing more transparency to the process of qualifying PROs and other drug development tools. A more workable standard that facilitates approval of well-defined and reliable PROs can and should be established. Additional resources for sealed and FDA's review divisions could lead to enhanced communication between these groups as well as increase capacity to coordinate effectively with sponsors regarding PROs.

In closing, it's important to note that to realize the changes suggested today, FDA must have sufficient resources to effectively evaluate patient- driven information. This includes ensuring that reviewers have the training and tools required to properly assess and analyze patient perspectives. Public-private partnerships could be a useful mechanism to enhance this regulatory science but we must adequately fund these initiatives to ensure they advance.

Again, I'd like to thank FDA for the

opportunity to participate in this meeting and present a patient-centered perspective of PDUFA and its programs. FasterCures looks forward to working with FDA and other stakeholders to enhance the existing benefit-risk framework, improve the science of patient input, and ensure FDA has the resources and tools it needs to effectively incorporate patient preference into regulatory decision-making. Thank you.

MS. TOIGO: Thank you, Maureen.

(Applause.)

MS. TOIGO: So that concludes our patient panel. Thank you to all of our presenters and we will take a 15-minute break and be back here at 10:55. Thank you. Reminder to order your lunches if you're going to use the kiosks.

(Whereupon, off the record at 10:39 a.m., and back on the record at 10:56 a.m.)

MS. TOIGO: Okay. This starts the beginning of our panel on healthcare professional perspectives and we have three speakers: Stacie

Maass from the American Pharmacists Association, James Baumberger from the American Academy of Pediatrics, and Richard Kovacs from the American College of Cardiology. So we'll start with Stacey.

MS. MAASS: Good morning. As Terry said, I'm Stacie Maass with the American Pharmacists Association, otherwise known as APhA. We are the Nation's largest and oldest professional pharmacy organization representing more than 60,000 pharmacists, student pharmacists, and pharmacist techs in all practice settings, so everything from hospital research as well as in the community setting.

Like others, I, too, would like to thank FDA for the invitation to provide our perspective on the implementation of PDUFA V to date as well as to offer some considerations to work on for PDUFA VI. We are pleased to see that the collaborative efforts through the PDUFA process between the Agency and stakeholders has resulted in improvements in many program areas over the

years. Further, APhA commends FDA for facilitating discussions amongst stakeholders well in advance of PDUFA VI. We believe that FDA's efforts to stimulate dialogue and discuss amongst stakeholders during PDUFA IV greatly improved the reauthorization process and will positively affect the PDUFA VI process as well.

Generally speaking, APhA believes that progress has been made on PDUFA V's goals. In 2012, we commented on several aspects of PDUFA V including drug shortages, REMS, biomarkers and pharmacogenomics as well as the Sentinel initiative. We appreciate the progress we have seen in these areas. However, as we all know, and many of us that make a living with healthcare, it's not static and due to the changing landscape and technological advances, certain facets of some of these areas may need to be revisited.

With regard to drug shortages, in 2012, APhA noted its support for many of the steps outlined in the legislation including early notification requirements, expedited inspections

and reviews of manufacturing sites and the establishment of a task force within FDA to improve communication. Three years later we believe these changes have helped address our Nation's drug shortage problem although clearly, we have not alleviated it. Our members have noted that they still encounter drug shortages, both brand and generic drugs which can create serious patient and provider access issues as well as unpredictable price spikes.

As we work on PDUFA reauthorization, we strongly encourage FDA, pharmaceutical manufacturers, and other stakeholders to focus on continuing to refine the processes and identify new solutions to prevent and manage these drug shortages.

With regard to REMS, APhA was very pleased with the inclusion of improvements to the REMS in PDUFA V. Since implementation began, we have continued to advocate for REMS programs that safeguard patient health and safety while limiting the burdens on the healthcare system and also

recognizing the important role the pharmacist plays in safe medication use as part of the patient's healthcare team. We hope to see continued progress as reauthorization approaches to best communicate to the patient information and education. REMS education initiatives are important for safe and effective medication use but improved educational resources for clinicians and patients are also needed for drugs that do not require REMS.

We encourage FDA and sponsors to consider whether some of the lessons learned through the REMS programs could be extrapolated into initiatives that improve medication safety on other classes of drugs and for example, for Rx to OTC switches.

We know FDA is aware but APhA would like to reiterate that the pharmacist's unique knowledge and expertise should be utilized in developing and implementing programs and initiatives to more effectively and efficiently

provide medication and related services to optimize the patient's medication use as well as their outcomes.

In the area of biomarkers and pharmacogenomics, APhA has supported the advances in the utilization of biomarkers and pharmacogenomics markers. As part of the patient's healthcare team, many pharmacists integrate pharmacogenomics into their practice to achieve and optimize medication use and, therefore, result in outcomes as well as patient safety.

As medications evolve to become more complex and more personalized, patients' counseling and education regarding medication regimens will likely become more imperative to the success of patient outcomes. Pharmacists have more medication-related education and training than any other healthcare professional and they, therefore, make the logical choice to provide care and services related to medications.

However, pharmacists face significant

barriers to providing these services and thus improving the patient's access and outcomes. For example, the pharmacist has significant challenges to having access to important information with regard to the patient's medical record. So we encourage stakeholders to continue to consider incentives and support enhanced coordination of care with the pharmacist to improve the medication adherence, safety in patient self-management as well as understanding as we go through PDUFA as well as other programs and related regulation.

With regard to the Sentinel program, APhA supports the continued improvement and enhancement of the Sentinel program and the adverse drug event tracking programs in general. Recently, in the context of biosimilar naming, suggestions had been made to addressing in other policy areas the improvements to the adverse drug error reporting system. We encourage FDA and sponsors to work together to evaluate these systems and to find workable solutions to any deficiencies rather than addressing them in other

policy areas.

Many of our member pharmacists and pharmaceutical scientists participate in practice-based research networks as we all as postmarket surveillance activities that produce valuable data about the safety and effectiveness of approved products. As FDA moves forward on pharmacovigilance issues, we ask that FDA solicit and incorporate feedback from the medication experts, the pharmacists and the pharmacy profession.

In closing, APhA again thanks FDA for the opportunity to provide a pharmacist's perspective on PDUFA IV today. We appreciate FDA's work on facilitating transparency and dialogue amongst stakeholders as implementation of PDUFA V continues as well as reauthorization discussions ramp up. We look forward to continuing to work with FDA, manufacturers, and other stakeholders as the process continues. Thank you.

(Applause.)

MS. TOIGO: Thank you, Stacie. James.

MR. BAUMBERGER: Good morning. I'm James Baumberger. I'm an Assistant Director in the Dement of Federal Affairs at the American Academy of Pediatrics, and thank you for having me here today to talk about the pediatric perspective.

The American Academy of Pediatrics is a non- profit professional medical organization of over 64,000 pediatricians including primary care pediatricians as well as medical and surgical pediatric subspecialists. Our mission is dedicated to the health of all children from infancy through adulthood, and it's in pursuit of that mission that AAP has led efforts to increase the number of drugs studied in children since the publication of its seminal policy statement in 1977 calling for a dramatic shift in how we approach pediatric drug development in this country.

The two pediatric drug laws, the Best Pharmaceuticals for Children Act, BPCA, and the

Pediatric Research Equity Act, PREA, have truly changed the way pediatrics are practiced in the United States. Prior to BPCA and PREA, upwards of 80 percent of drugs used in children were not studied in children and were, therefore, not labeled for their use. Now, today, that number is much closer to 50 percent. So we've certainly come a long way. It's a mark of success but we have a long way to go.

BPCA is a voluntary incentive of six months of additional marketing exclusivity for conducting FDA-requested studies in children, and PREA is a premarket pediatric studies requirement that applies to new drug applications as well as supplements. Combined, BPCA and PREA have led to 580 labels changed with new pediatric information.

FDASIA permanently reauthorized BPCA and PREA in 2012 so this gave children a permanency seat at the drug development table. And FDASIA also made numerous important changes to the operation of BPCA and PREA.

So in terms of the Prescription Drug

User Fee Act, pediatrics has never been directly a part of the user fee agreement that FDA has negotiated with industry. However, PDUFA has always been the legislative vehicle for reauthorizing BPCA and PREA since its inception. So pediatrics isn't specifically a part of the user fee agreements so there are no specific pediatric timelines, fees, or requirements that are within the user fee agreement itself.

However, over the years, FDA has been given expanded important additional responsibilities to implement BPCA and PREA. FDASIA added some. And in the coming years, FDA will have additional responsibilities that they'll need to take on in terms of pediatrics including greater collaboration with international regulators across the globe on pediatric issues as well as adapting to new and developing, emerging science in pediatric drug development.

So AAP believes that it is essential that FDA be adequately resourced to carry out all of its responsibilities in the pediatric program

and also be able to work predictably with sponsors on pediatric issues.

So now I'm going to talk about some of the really important issues that are facing the pediatric program, and the first is beginning pediatric drug development earlier in the process. Prior to FDASIA, the pediatric study plans under PREA were not required be submitted to FDA until the time of the submission of the adult application, until the end of phase three in the drug development process. FDASIA changed that and moved it up with a new requirement that initial pediatric study plans be submitted to FDA at the end of phase two.

For BPCA and PREA, there are no specific timelines for when the agency has to issue a written request and no specific timelines of when a division or a sponsor needs to initiate that process. But AAP does believe that in some cases, there is no reason not to start pediatric drug development earlier in the process, particularly for drugs for serious and life- threatening

conditions. So we don't want resources to ever be a barrier to achieving this goal. So lack of resources should not be a barrier to ensuring that divisions and sponsors can talk about pediatric development as early as possible in the drug development plan, even before the end of phase two if necessary or if needed for a specific drug. We also don't think resources should ever delay the issuance of a written request that is ready to be issued.

So next, I want to say a few words about the timeliness of the completion of PREA's requirements. So responding to a large number of delayed deferred PREA assessments that were classified by the Agency as delayed, FDASIA addressed this issue by doing two things. First, it allowed FDA to extend PREA deadlines if there is good cause to do so. And second, it gave FDA a new enforcement tool to deal with PREA requirements that were -- did not have good cause for being delayed. So that enforcement comes in the form of a non-compliance letter which is a

letter FDA issues to a sponsor if they have unnecessary delayed pediatric studies. Since the passage of FDASIA, FDA has issued 16 such non-compliance letters and we thank FDA for going through the backlog of deferred studies. But to our knowledge, today none of these letters have yet to result in completed pediatric requirements for those specific drugs. So we look forward to continuing to monitor this new enforcement mechanism to ensure that it's meeting the goal of ensuring more timely completion of pediatric study requirements.

Next, I want to talk a little bit about neonates. So while BPCA and PREA have been remarkably overall, they've been less successful, and that success is not always translated all the way down to the neonatal population, our youngest children. Still today the majority of drugs used in the neonatal population are not adequately suited in neonates and not labeled for their use. FDASIA addressed this issue and called attention to this issue in two ways. First, it's required

now that all written requests need to include a requests for studies in neonates or it needs include a scientific rationale why it chose not to do so.

And second, there is a requirement that FDA hire a dedicated neonatologist, a full-time dedicated neonatologist to assist in the review of pediatric study plans and the development of written requests specific to neonates. FDA does have a couple of neonatologists on staff. They are dedicated people but they are not dedicated in their jobs in neonatology; so unfortunately, FDA does not yet have a full-time neonatologist on staff to do this work but we're hopeful that this will happen soon.

Next, adapting to the evolving science, PREA is only -- can only be triggered when an adult indication for a drug can exactly mirror a potential indication for that drug in children. Yet as more and more drugs are being developed for specially targeted indications, there is a greater risk that these drugs will not be relevant, the

indications themselves will not be relevant to pediatrics and, therefore, will result in a waiver under PREA. In addition, as drugs are being developed for specialty targeted populations in addition to indications, there is also an additional risk that drugs will be completely exempt from PREA based on their statuses, orphan drugs.

So we think we need to look critically at PREA and ensure that PREA -- to look and see how PREA may need to be altered to adapt to evolving science and drug development. And this is particularly important in the pediatric cancer space which is going towards increasingly targeted treatments. AAP is a member of the Alliance for Childhood Cancer which is an alliance of professional organizations and patient advocacy groups that work in childhood cancer issues. BPCA and PREA have been crucial issues for the Alliance since its founding and the Alliance has created a working group which AAP is participating in to critically evaluate BPCA and PREA in the pediatric

oncology space and make recommendations for how they may need to be improved.

Next, pregnant and breastfeeding women: We have even less information in drugs in pregnant and breastfeeding women than we do in children. Still today there is very little information on how drugs work differently in pregnant and breastfeeding women and also how women taking those drugs then may or may not be affecting the fetus or their nursing babies. So AAP has joined with several other groups to the Coalition to Advance Maternal Therapeutics. The American College of Obstetricians and Gynecologists are also members as well as the March of Dimes and the Society for Maternal-Fetal Medicine.

So as first steps, we've been urging better reporting from FDA on the number of drugs that are studied in pregnant and lactating women, and we'd also like FDA and other federal agencies to improve how they collaborate on activities related to the safe and effective use of drugs during pregnancy and breastfeeding.

And lastly, I'll just mention that FDASIA created a new report, required FDA every five years to do a report on BPCA and PREA. That first report is due next summer, in July of 2016 and hopefully that report will address many of the issues that I've addressed here today. But I also -- we also hope that the report would contain an honest assessment of FDA's ability to meet all of its responsibilities under BPCA and PREA under its existing resources. And if FDA feels that those resources are not sufficient to meet those responsibilities, we would urge that FDA either request funding either through the user fee program or through the annual budget process to help fund any additional needed activities.

Just lastly, I wanted to end with a thank you to FDA for all the work that it's done to make BPCA and PREA a success and really change therapeutics for children, so thank you very much.

(Applause.)

MS. TOIGO: Thank you, James. And our last speaker is Richard Kovacs from the American

College of Cardiology.

MR. KOVACS: I'd like to thank the FDA for inviting the college to represent itself. We are especially proud of the fact that Dr. Califf is a member of the American College of Cardiology and the College asked me to ensure that his dues are paid up, and although he moved from the front row to the back row, he assured me that he continues to be a card- carrying member of the College.

These are my disclosures and in terms of full disclosure, I spent a part of my career in large pharma so I represent the primary caregivers, the team that cares for your cardiac disease. So it is highly likely that you, if you or yours face a serious heart problem, that it is more than 90 percent likely that you will meet one of us in the course of that care, and we stretch across the country and around the globe.

The College has just embarked on a five-year strategic plan which closely aligns with the National healthcare goals to improve care, improve

outcomes, improve population health, and do so at less cost. More importantly, the College has developed tools and we've heard a bit of registry speak this morning but the ACC, I believe, is probably the furthest ahead and the longest running rich patient-based cardiovascular registries in multiple procedures and disease states. The registries supplement other forms of data and reach thousands of hospitals, millions of patient records, and provide a rich source of confirmatory data in the real world for what we find in randomized clinical trials. And already we have partnered with the FDA and I'm sure many of the FDA representatives recognize the role of the College in a number of efforts to improve drug development and drug safety in the United States.

The goals of the College align quite nicely with the goals that are being aspired to in this room for our registries especially to become more patient- centered, to become the platform for clinical trials and effectiveness research, and to provide for postmarket safety surveillance.

So I will move now to where we have been and where we would like to go. Clearly, we're doing something right. The most recent mortality statistics in the United States, these are just recently published but they lag a little bit as many of these statistics do, show decreasing numbers of death from cardiovascular disease for both men and women in the United States. And during the current cycles, we've seen about a third reduction in the burden of death from cardiovascular disease despite an aging population.

In addition, the cardiovascular care team has been very happy to see new treatment for stroke risk reduction, for heart failure just within the last few days, and the promise of even more cholesterol- lowering drugs for the tens of millions of patients in the United States that need preventive therapy.

We have three recommendations going forward. Number one is to advance regulatory science. This graph taken from a paper by Dr. Ray

Woosley shows that regulatory science is a relatively recent development in what we have looked at in terms of pharmacology and safety pharmacology, pharmaco-epidemiology and it has enormous promise for the future. In addition, it has effects beyond what may be apparent to people who deal with drugs and drug safety, two examples of which are the output from what I do for a living, which is the pro-arrhythmic effects of non-anti-arrhythmic drugs, something that's dealt with within the FDA by the interdisciplinary review team and has led to a very scientific approach to this problem. These data have been used by others, in one case by the Mayo Clinic by Mike Ackerman's (ph) group, and the other case by my own group at Indiana University to develop safety systems in our medical care systems to provide real- time automatic safety for patients that may have to take these drugs.

In addition, Dr. Woosley's group at the University of Arizona has been able to maintain a website for patients and providers that provides

up to the minute incontrovertible data based on this regulatory science that allows people to make intelligent choices on drugs if they have risk.

So the extent of regulatory science is beyond what may be seen and may provide some additional evidence to continue to fund and expand this particular area.

Second, we recommend that the drug safety system be modernized and we have literally taken a page from the device side. The American College of

Cardiology recognizes that drug safety or device safety is a cycle with many components and many failsafe systems: clinical registries, clinical reporting at the bedside, all of those and other safety surveillance systems are part of that and we urge that the drug safety system continue to be refined and modernized using new technologies and new data.

It was mentioned that one of the ways to do this is to run trials within registries. The College has done that. The FDA is aware. And

this is just one example of looking at antiplatelet therapy in real-world registry data to determine safety and effectiveness of the therapies that we give at the bedside every day.

And finally, and to reinforce the prior panel, the College, as all caregivers are, we need to listen to our patients. The College is committed to the closure of racial and ethnic disparities in care, to include more cardiovascular disease research in women, and to perform safety surveillance in special populations. This requires all of us, not just some of us and we should be utilizing our registries. They have been mentioned several times but they provide a rich and continuous source of patient data that has that clinical richness in the clinical detail and can be adapted and will be adapted for patient-reported outcomes.

So in summary, the American College of Cardiology would recommend number one, to increase funding for regulatory science activities, of science in its infancy. We would like to continue

to explore these novel techniques for postmarket surveillance and patient-centered data generation, and we offer our registries as a platform for doing that. We also, and I didn't touch on it as much, but we also would like to explore more in the way of data transparency and we would offer the knowledge and expertise of our specialty society in this worthwhile endeavor. Thank you.

(Applause.)

MS. TOIGO: Thank you, Dr. Kovacs, and thank you to our health professional panel and we'll move to the final panel for the morning, and that's the regulated industry perspectives. Okay. First, we'll hear from PhRMA. Sascha.

MR. HAVERFIELD: Thank you. Good morning. I won't make you do the same as Marc did earlier but I do want to get your attention. So I'm Sascha Haverfield. I'm the Vice President for Science and Regulatory Advocacy at the Pharmaceutical Research and Manufacturers of America.

PhRMA is a trade association

representing the leading biopharmaceutical companies devoted to discovering, developing innovative medicines that enable patients to live longer, healthier, and more productive lives. PhRMA and its member companies support a strong, vibrant, and science-based FDA funded through a combination of appropriated funds and a robust PDUFA program. Discovery, development and delivery of safe and effective innovative medicines to patients is the core mission of our members. And achieving this goal depends on a FDA that advances the public health by providing timely science-based regulatory decisions.

PhRMA has been a strong supporter of and participant in the Prescription Drug User Fee Act since its inception in 1992. PhRMA is pleased to participate in today's public stakeholder meeting and appreciates the opportunity to respond to the FDA's request for comments on the overall performance of PDUFA V.

The FDA's mission is to protect and

promote the public health by ensuring the safety, efficacy, and quality of human drugs and biologics. Biopharmaceutical companies share the Agency's commitment to serving the public health. We do this by researching safety, efficacy and quality of human drugs and biologics. Biopharmaceutical companies share the Agency's commitment to serving the public health. We do this by researching, developing, manufacturing, and delivering innovative, safe, and effective medicines to treat devastating illnesses such as cancer, diabetes, and Alzheimer's disease.

Our understanding of many diseases has increased tremendously in recent years and the potential public health implications of the science we utilize have never been more promising. With more than 7,000 medicines in development globally, biopharmaceutical researchers are working to turn potential treatments into FDA-approved medicines that will help patients. This work not only benefits patients directly but the U.S. economy as a whole. Working with scientists,

physicians and healthcare professionals in every state to develop and test new medicines, the research enterprise touches communities across the country creating 3.4 million direct and indirect jobs and investments in local economies.

PhRMA members have invested more than half a trillion dollars in research and development since 2000 including an estimated $51.2 billion dollars in 2014 alone. This investment represents the largest R&D commitment of any business sector in the U.S.

Only one out of thousands of promising preclinical molecules and less than 12 percent of candidate medicines that enter phase one clinical trials will ultimately be approved by the FDA. This attrition rate is one reason that the investment in R&D is so great in our industry. Thus, we assume great risks in order to deliver great benefits to patients. It follows then that our industry has a tremendous stake in facilitating timely science-based FDA regulatory review and approval of safe and effective

medicines to address patients' needs.

PDUFA has played a critical role in bolstering the FDA's ability to regulate safe and effective medicines for patients. PDUFA was created in response to a perilous bottleneck of new drug approvals in the late 1980's and early 1990's that left patients waiting and sometimes dying while an understaffed and underfunded FDA struggled to review new drug applications.

As you've already heard earlier today, in 1992, Congress passed the first Prescription Drug User Fee Act to meet urgent patient needs for timely approvals of life-saving medicines. For more than 20 years, PDUFA has helped the FDA fulfill its central mission to protect and promote the public health by allowing the Agency to keep pace with the rapid increase in the number and complexity of innovative 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 1998 -- in 1989 --

I'm sorry -- FDA's human drug review program was staffed by approximately 1,900 employees. By 2014, the human drug review staff had grown to more than 3,700. The infusion of user fees to support the FDA's review process has meant that the median time needed to review a new drug application or biologic's license application has been reduced significantly from 29 months in 1989 to 12 months for standard review of new molecular entities in 2014.

Priority review NME products, drugs that offer major advances in treatment or provide a treatment when no adequate therapy exists now see a median review time of just 6-1/2 months. The new drug application process has also become more predictable as a result of PDUFA. Under PDUFA V, FDA and biopharmaceutical companies agree to establish a new NME program, the program with a goal to improve the efficiency and effectiveness of the first cycle review process and decrease the number of (inaudible) cycles necessary for approval, ensuring that patients have timely

access to safe, effective, and high-quality new drugs and biologics. The NME review program is built on a foundation of effective two-way communication throughout the regulatory review process and promotes greater regulatory transparency and predictability.

A predictable review process that allows for timely responses to FDA'S medical and scientific questions and appropriate regulatory transparency for sponsors can help ensure timely patient access to safe, effective, and high-quality new drugs and biologics. To date, the program has demonstrated meaningful progress and increasing the likelihood of first cycle approval for NME, NDA, and original BLA applications.

Despite the clear progress that has occurred under PDUFA V, including advances in regulatory sciences, many challenges still remain. For example, it is increasingly important for researchers as well as FDA to gain a deeper understanding of diseases and condition elements that have greatest burden to patients. Under the

PDUFA V patient-focused drug development initiative, FDA is collecting patient input through a series of public meetings and specific disease areas. This includes patient perspectives on disease severity and unmet medical need. However, additional clarity is needed on how to translate patient preference information into tangible outcomes to inform clinical research and the regulatory review and decision-making processes.

Advancing the science of patient input will require the engagement of all relevant stakeholders. We must build on our efforts under PDUFA V to appropriately incorporate patients' perspectives into regulatory decision-making by advancing the science of collecting, analyzing, interpreting, and integrating broad-based disease state patient information into regulatory processes. As such, PhRMA will advance and support policies in PDUFA VI that better integrate the patient perspective in drug development and regulatory decision making, enhance the scientific

expertise processes and tools FDA uses to regulate increasingly complex medical products and public health issues, and promote the long-term stability of the PDUFA program by improving its financial transparency, efficiency and accountability and ensuring that FDA can recruit, hire and retain a highly skilled workforce its public health mission.

By focusing on these principles, PDUFA VI can play a critical role in continuing to advance an effective science-based U.S. regulatory review program that helps ensure that biopharmaceutical companies may continue to bring innovative medicines to patients in need. Both the FDA and biopharmaceutical companies have a significant responsibility to safeguard and improve public health. It is our shared responsibility to ensure that America's healthcare system stays at the forefront of quality and innovation. Supporting the FDA's ability to perform its critical review and subsequent monitoring of new medicines in a timely and

effective manner is one way our industry can continue to serve patients.

PDUFA's 23-year history has paralleled the most productive and innovative generation of new drug development. From novel vaccines to breakthrough medicines and target therapies, the past two decades have seen a revolution in innovative medicines addressing unmet medical needs. FDA can be proud of its leadership and helping biopharmaceutical companies deliver these therapeutic advances to the public by vigilantly watching out for their safety. The lives of countless children, adults, and aging Americans have been enriched and extended by the hundreds of novel therapeutics that have passed through the FDA's regulatory review programs since PDUFA's inception in 1992.

It's been largely through the added resources afforded by PDUFA that the FDA has been able to regulate effectively during this landmark era of transformative, scientific, and medical

advances. The optimal review and approval process is one that is both efficient and judicious and that integrates the patient perspective by advancing the science of patient input. Public health and safety are best serviced by a science-based balance between the need for timely and vigorous premarket review and postmarket surveillance. PDUFA has afforded the FDA the means to achieve that optimal balance which is why PhRMA supports a well-funded, science-based FDA supported by a combination of appropriated funds and a strong PDUFA program.

Thank you for your time and thank you for the opportunity to be here.

MS. TOIGO: Thank you, Sascha.

(Applause.)

MS. TOIGO: Next, we'll hear from BIO. Kay Holcombe will present.

MS. HOLCOMBE: Thank you. On behalf of the biotechnology industry, I thank you for the opportunity to comment on the success of PDUFA and to provide you some of our thoughts as we move

toward the authorization of PDUFA VI.

BIO is a trade organization that represents biotechnology companies, academic institutions, state biotechnology centers, and related organizations in the United States and globally. BIO members are involved in the research and development of innovative biotherapeutics, agricultural, industrial, and environmental biotechnology products. We fully support timely reauthorization of PDUFA and we look forward to working closely with FDA, Congress, and other stakeholders to enhance the program further.

PDUFA has been successful. Since its inception in 1992, PDUFA has been widely credited for facilitating earlier patient access to more than 1,200 innovative medicines while preserving FDA's rigorous standards for safety and efficacy. PDUFA V made meaningful improvements and PDUFA VI should build on that record of success. For example, the NME review program has stabilized review times and achieved historic first cycle

approval rates.

PDUFA V also took the first steps toward a new and critically important patient-focused drug development paradigm intended to help understand patient views of disease and incorporate those perspectives into the regulatory process through a structured benefit-risk framework.

Under PDUFA V, FDA also committed to a philosophy of timely, interactive, scientific communication during drug development and to the identification of and training in best communication practices.

The successes under PDUFA V have been substantial but there have also been challenges. For example, a portion of industry-funded user fees were unavailable to the Agency during the government-wide sequestration in the first year of PDUFA V. We cannot let this happen to FDA again. This and other obstacles prevented FDA from meeting its hiring goals to bring new scientists and managers into the Agency to support a number

of PDUFA V programs such as some important regulatory science initiatives. Enhancement in the FDA's ability and expertise related to the use of patient-reported outcomes, biomarkers as surrogate endpoints, innovative clinical trial designs, and pharmacogenomics data will have long-term, positive impact for patient-centered drug development and regulatory decision making.

The inability to achieve this enhancement is concerning and as PDUFA VI process moves forward, FDA and stakeholders need to work together to define the causes, understand them clearly, and try to address them. To ensure that PDUFA continues to evolve to the benefit of patients, the biopharmaceutical industry will be guided by three over-arching principles which BIO shares with PhRMA. First, better integration of patient perspectives into drug development and regulatory decision making. Specifically, as the science of patient preference assessment evolves and matures, it is essential for FDA and stakeholders to work together to drive the process

forward from an often anecdote-driven approach to a systematic and data-driven process that can occur at each stage of drug development and review.

It is crucial that FDA, patients, and industry work together to evaluate and use appropriate scientific methodologies for assessing patient views and perspectives and leverage FDA's structured benefit-risk framework throughout a therapy's life cycle. Clear guidance and established processes on patient preference assessment methodologies and data should translate patient feedback into new and effective drug development tools such as qualified PROs and biomarkers.

Second, enhancement of FDA's scientific expertise processes and tools. PDUFA V made significant changes that helped to enhance the FDA review process. This is good news. However, it is equally important that PDUFA provide FDA with the tools and scientific capacity necessary to help streamline and modernize the clinical

development process. The process must embrace new, modern research methodologies such as innovative clinical trial designs, new methods of statistical analysis, and the use of big data and real-world evidence to inform both the premarket and postmarket phases of drug development and review.

I want to focus on just one example of such a tool. BIO believes that communication during drug development is a tool that can both enhance the FDA review process and help address the length and high failure rate of drug development. The communications program under PDUFA V recognized this and took steps in that direction. Robust, scientific communication can lead to a better understanding of FDA's expectations, improve the ability to resolve issues and address scientific questions that do not necessarily rise to the level of requiring a formal meeting with the Agency. It is undeniable that drug development fares better for both FDA and sponsors when there is productive

communication.

With this in mind, over the past year, BIO has conducted a survey designed to understand our member companies' experiences in interacting with the Agency during various stages of drug development. Early results from 324 clinical development programs indicate that about half of the surveyed participants report that their interactions with FDA are very beneficial and productive while half of the participants state there is room for improvement. Additionally, the survey indicates that there is considerable variability in communication practice and timeliness of communication across review divisions. The survey identified several review divisions that excelled in communicating with sponsors interactively and productively. We continue to share these survey results with survey participants and with FDA so that we can move together in PDUFA VI to identify best practices for communication that can be emulated across all FDA review divisions.

Our final overarching principle is ensuring the long-term stability of PDUFA. We must continue to support the sustainability of the PDUFA program so it will benefit future generations of patients and drug developers. We also must ensure that FDA has the hiring flexibility and human resources management processes necessary to recruit and retain world class scientists and managers. Finally, we must continue to work with Congress to guarantee once and for all that user fees are not subject to any future sequestration.

Thank you for the opportunity to present BIO's views on PDUFA which has been a win-win for patients, industry, and FDA. We look forward to working with FDA, other stakeholders, and Congress to ensure timely reauthorization of this program.

While I don't want to engage in unnecessary hyperbole, I believe firmly that for a patient with an unmet medical need, a safe and effective FDA-approved therapy available in time to make a difference in her life is that patient's

Pluto fly-by. Although drug development is not rocket science, we at BIO are firmly committed to being on that rocket that makes that possible for every patient and together with PDUFA and working with patients and FDA, we can make that happen. Thank you.

(Applause.)

MS. TOIGO: Thank you, Kay. So our last speaker for the morning is Michael Werner from the Alliance for Regenerative Medicine.

MR. WERNER: Thank you. Yes, the last speaker of the morning, the prime spot. So thanks to FDA for holding this public meeting and for inviting me to speak to you this morning.

My name is Michael Werner. I'm the cofounder and Executive Director o the Alliance for Regenerative Medicine. The Alliance is a multi stakeholder group representing life sciences companies of all sizes and stripes but also patient advocacy groups, academic institutions, clinical centers, and investors and really, we see ourselves as representing the community of people

who are interested in researching commercialization of regenerative medicine and advanced therapies. And we define that to include cell therapies, gene therapies, immunotherapies, and other advanced therapies. And I will say at the beginning that we are very pleased and proud of our relationship with the FDA. One of the first things we did when we started in 2009 was come and meet with the senior leadership of the Agency, and we talked about that we really have shared goals which is to make sure that safe and effective products get to patients as soon as possible. And we have had and still have a whole series of ongoing projects on many of the points that we've talked about this morning about communication or regulatory science or other issues with the Agency that have been big successes.

And certainly, we also want -- I want to say that from a perspective of resources and staff, that is also something that our organization feels very strongly about, that is

critical for the Agency going forward, especially as the technology becomes more complex and the demands on the Agency get greater.

So I mentioned that we're a multi stakeholder group. We are the global advocate for regenerative medicine and advanced therapies and we foster research and development and investment and commercialization of transformational treatments and cures for patients worldwide. We work on education and advocacy.

So many of you, what's been really satisfying about working with ARM is that over time, I have to say these things, you know, less and less which is now, I think, more and more people are realizing the promise of this technology. We all know that there are lots and lots of really good drugs out there and good treatments out there. Many of them though for people with chronic diseases are still what would be called palliative, which is we're treating symptoms; we're, of course, making their life better, we're helping them get back to work or

what have you, but they're not cures and they're not necessarily addressing the progression of disease, and we have a very costly healthcare system as a result of that and, of course, many other factors.

We believe that these advanced therapies provide the next frontier for patients, potentially curing devastating diseases, particularly in unmet medical needs areas. And we define this group of technologies as products that augment, repair, replace, or regenerate cells, organs, and tissues throughout the body. So, some of the areas that we're talking about that many of you have heard of, certainly the CAR-T and other adopted T-cell therapies for cancer; various gene therapy approaches; various cellular therapy approaches; and tissue engineering. All of these are technologies being researched, commercialized, invested in, and paid attention to by members of our group.

And we're not really an emerging field anymore. There are now 580 companies worldwide

that comprise this sector and there's about 60 products on the market and about almost 500 now clinical trials in phase one, phase two, and phase three.

So that's kind of about ARM and about the technology so as we talk about PDUFA, we think that PDUFA should be part of a national strategy in the United States to support these technologies. When you think about the promise, you think about what can really be done, it makes sense for our Nation to really focus its energy on these issues and on the ways to promote the technology. This is not a new concept. We have national strategies in this country on things like access to broadband technology, on semiconductor technology. This is something we've done before when we've recognized that there is a platform technology that has all kinds of positive benefits, and we believe that regenerative medicine advance therapies is that kind of technology in the healthcare sector.

So we believe there needs to be a focus.

Other countries have recognized this. Japan, China, South Korea, and Canada all have designated strategies in this space so we think it's important not only to enable patients to get products but it also allows our country to remain at the forefront of the national and the global stage in these areas and certainly, PDUFA, as part of a predictable, clear, and efficient regulatory pathway to market is part of that strategy. And so that's why we're here today.

We have a couple of specific ideas that I wanted to raise. One is about a standards coordinating body. Another has to do with qualified regenerative medicine products, and the third is about improved coordination and communication among FDA review centers.

So let's talk about standards first. The introduction of standards or greater standardization in this field has been identified by FDA and by many in the stakeholder community as critical to getting us to sort of the next phase of product development. Whether we're talking

about cell characterization or potency assay development or the like, the need for standards clearly is present. We've been working with FDA, with NIST, with standard-setting bodies, academia, and others to try to identify how we can develop standards and have them proliferate throughout the world. The idea that we are promoting is a standards coordinating body here in the U.S., so it's not a government standard setting operation. It is, however, where government and the private sector can facilitate the development of measurement, the development of standards, be a clearinghouse and have those be incorporated into the regulatory process. Whatever regulatory science needs to happen will happen and this can become part of the regulatory approval process so that we can provide greater efficiencies in that process for product developers.

We advocate for something called a qualified regenerative medicine product, so this is about improvements to the approval pathway. There are certainly lots of historical precedents

for -- it's not a new pathway per se. Many of these products are BLA-approved products. Some are medical devices. Some are combination products. We're not thinking that there needs to be a whole new pathway but we do think there should be a way for regenerative medicine products targeted at serious or life-threatening illnesses, particularly for medically unmet needs, that there can be some kind of a designation as a qualified product which will provide opportunities for improved communication between the sponsor and the agency, particularly as it relates to expedited review opportunities.

And then finally, many -- Kay talked about this a little with BIO, a lot of our member companies and sponsors have talked about ways to improve communication with the Agency and actually, we have a project with the Agency about that but this is also -- there has also been an identification of the need to improve communication within the Agency, so communication and coordination between or among review centers.

So this is particularly an issue, of course, if you have a combination product as many regenerative products are but even if you don't, if there's a need for a consultation with a different FDA review center, for example, the experience has been that sometimes that process isn't as efficient as it should be and there are delays and the like. And we are recommending the development of a new framework to facilitate consistency and efficiency among the review divisions.

So in summary, I'm going to join the chorus and say that we believe that PDUFA has been a tremendous success over the years and PDUFA V is no exception. The improvements in regulatory science, the projects on the new expedited approval pathways and the like have been tremendous. And we think we can build on those to enable these new exciting and innovative technologies to get to market even more quickly, and we look forward to working with stakeholders and the Agency and Congress as the process moves

forward. Thanks very much.

(Applause.)

MS. TOIGO: Thank you, Michael. So that concludes our morning session. In the afternoon, we'll have one more panel and we'll hear from Dr. Woodcock. And I know we have at least one public speaker, so if you want to speak in the public session, you need to register before lunch. And we'll see you back at 12:45.

(Whereupon, off the record at 11:56 a.m., and back on the record at 12:45 p.m.)

MS. TOIGO: Okay. Good afternoon, everybody. We're going to get started. We have our Panel 5 if you look at your agenda, and that's our scientific and academic expert perspectives. We've got five speakers who are going to present during this panel. And then following the panel, Dr. Woodcock will provide some closing remarks. And then as I mentioned, we have five speakers signed up for the open public hearing and they'll each have about five minutes. And that should get

us to two o'clock. So I'm going to start with Greg Daniel who is going to speak on behalf of the Center for Health Policy at Brookings. Greg.

MR. DANIEL: Thank you. Good afternoon, everybody. Thank you for coming back from lunch.

I would like to talk a little bit about the PDUFA V goals. We've seen this morning some presentations and overwhelmingly a lot of success has happened in just getting halfway through PDUFA V. And something that struck out at me as I watched some of the panels this morning through the webinar is that really does seem to be consensus that improved communications between the review teams at FDA and the sponsors is really happening now under PDUFA V, and this is leading to first cycle review rates that are much higher than before. Beyond this, in our own experiences working with the Agency at Brookings, it really has demonstrated forward thinking within the Agency as it approaches a range of scientific and regulatory issues. Just to cite one example, implementation of the breakthrough therapy,

development -- or designation program which is not part of PDUFA V per se, has drawn a lot of praise from stakeholders across the spectrum.

PDUFA VI provides an opportunity to build upon the successful work already underway at the Agency, and I'll touch on a few key areas that Brookings has had some work in as well as touch on a few areas that aren't included in previous PDUFA reauthorizations that we might consider as being appropriate at this stage.

So one of the areas that we've been working with the Agency is in these PDUFA V goals and we've seen that under the commitment that the Agency has is to develop a structured benefit-risk framework within the drug review process, requirements being met that are enclosed under the patient-focused drug development program, and by-and-large, those activities are proving to be successful. And I think by the end of the period, instead of the committee patient-focused drug development meetings, the Agency will have completed 24, so congratulations. That's a great

accomplishment. It's also a lot of resources. A very resource-intensive process.

Moving forward, our perspective is that increased focus on systematic collection of patient experiences targeted to specific therapeutic area needs, this is not as simple, as you all know, as creating a template that will be used for every disease area. Collecting patient experiences are very therapeutic area specific and it's challenging, and it takes a lot of resources to implement something like that, and continued support for that is critical.

More formal guidance on the process for leveraging externally-led groups or externally-led patient-focused drug development meetings might be a way to scale and keep this program sustainable. As I mentioned, it's a lot of resources to design and conduct these patient-focused drug development meetings, and the meetings themselves are a first step. A lot of work needs to happen after those meetings to systematically incorporate what we're learning from patients in those meetings into FDA

processes and approaches and decision-making. Support for more guidance on how externally -- external groups can help support this would be one way to scale this program.

A lot of effort has been focused on patient- reported outcomes instruments. Some of the commitments included develop clinical and staff capacity to better respond to submissions that involve PROs, hold a public meeting to discuss qualification standards for PROs including within the drug development tools. And PROs are an important aspect. For a patient to engage in decision-making with their provider and to understand whether or not that they're considering taking has been evaluated on outcomes that are meaningful to patients, evaluated on outcomes that actually come from patients themselves is critical. And processes to get -- encourage more use of PROs within labeling is important, and for PDUFA VI, focus might be on obviously the sealed group within the Agency is doing a lot of great work. They do need additional resources to

continue to standardize the way the PROs are being developed and qualified. Additional resources for standardizing how the review teams across therapeutic areas are interpreting evidence from PROs and establishing the evidentiary criteria critical.

One area that FDA has already begun work in is developing the clinical outcome assessment compendia. This is a compendium that PROs that have been qualified, will include PROs that are in the process of becoming qualified and PRO also instruments that haven't been qualified yet that have been used in previous drug development programs and used in labeling. This is an important aspect because what we've heard from industry sponsors and others in the field, it is that it's hard to understand which instruments can be used, which instruments are acceptable for a particular endpoint and context of use. And if an instrument is not acceptable, what methodological changes, modifications to an existing instrument would make it fit for purpose. That's an area

that does need a lot of support nad more work and potentially next stages of the COA compendium can begin to outline a research strategy to identify how particular instruments could be made fit for purpose where the methodologic resources should be concentrated in order to improve a larger compendium of instruments that could be used to support labeling.

A lot of work, as we heard this morning, in biomarkers has happened, a lot of great work in terms of qualifying the first PRO tool, the exact PRO for chronic pulmonary disease. And moving forward, continuing to build a framework for evidentiary standards for qualification will be important. One thing that we at Brookings continue to hear from expert stakeholders across the spectrum is that, you know, nobody is using the term "biomarkers" in the same way. One biomarker isn't the same as all other biomarkers. There are different kinds, predictive and prognostic biomarkers, surrogate endpoints are different, and all of these types of biomarkers

can have very different roles in facilitating and supporting more efficient drug development programs, and the evidentiary criteria for using them and qualifying them are different. And so one first step in making further progress on this could be to come together on a common lexicon or at least understand more standard definitions for what these biomarkers are and what the evidentiary criteria is for using them in drug development programs and for qualifying them.

Additional resources in FDA leadership could help to encourage and promote pre-competitive collaboration and technical performance so that groups that are working in a space like the PRO -- or I'm sorry, the biomarker consortium and groups at critical path institutes -- they're all doing great work in these areas; they're not necessarily well-coordinated and there could be an effort led to help coordinate the groups working in biomarker development so that their learnings can be shared and so that we're not duplicating efforts.

And so finally, Sentinel was mentioned this morning. There were some PDUFA V commitments with regard to Sentinel. That is a growing and evolving program. It's currently being used by the Agency in safety surveillance activities. The system itself is evolving. It continues to evolve as electronic healthcare data evolve, as claims evolve, as more and more provider groups are using electronic medical records. Continued support and progress in making sure that Sentinel can benefit from those additional data sources, new methods for analyzing safety signals like the prompt tool which is a prospective monitoring tool that's been developed under Sentinel, all of these are great examples of progress. Continued support for that program to expand the types of producers that it could analyze under surveillance activities would be important too. This includes medical devices where we now have a UDI rule, which is a unique device identification rule. As those UDIs become more used in the electronic medical records and claims data, they can be brought into Sentinel in

establishing methods to analyze device surveillance and incorporating new types of data into Sentinel will be an important aspect. Leveraging the system for other uses -- FDA can play a leadership role and help facilitate how the system that it built can be used in other areas of healthcare including public health surveillance, including supporting efforts and facilitating uses of the Sentinel system by drug sponsors who are meeting their postmarket requirements or commitments that might be able to use the surveillance system as part of their requirements for, you know, tracking and monitoring safety events. This is being conducted by the Reagan Udall Foundation under the IMEDS program but will take continued support and leadership from the Agency as well.

And so on my last few slides, I'd like to touch on two critical areas that might -- in two minutes or less -- might -- we might consider as something for PDUFA VI and because we've seen all of the previous PDUFA commitments have been

almost entirely focused on premarket process. However, over the last several years, investments by industry, specialty societies, hospital systems, and payers, groups like PCORI, and the FDA are building large national systems to generate evidence on safety and effectiveness in the postmarket setting.

A shift in user fees to improve the process and quality of drug development by identifying opportunities to fill evidence-sharing gaps that remain upon approval is one way -- and one way to do this would be to explore opportunities to bridge premarket data collection to postmarket data collection. And this builds off of some of the comments we heard from Allan Coukell this morning at Pew. And Jeff Allen at Friends of Cancer Research also supported the idea of thinking through how postmarket data systems could help build a standing infrastructure for more efficient continued learning from premarket to postmarket. This can help safety surveillance activities as Sentinel is always doing.

Post approval studies, if there was a standing infrastructure, those could be conducted, started more efficiently, and more efficient monitoring when needed to help facilitate further implementation of expedited drug development review programs.

Opportunities for more relevant data to augment and support clinical trials is also important. We're not talking about replacing clinical trials. What we are talking about is new opportunities to bring additional evidence to the Agency as its making decisions and evidence that cover the actual impact of these products in the real world.

The next round of PDUFA commitments might include a program to help figure some of this out. And so what I mean by that is let's explore how pragmatic clinical trials -- these are observational type studies because they are less restrictive than clinical trials but they are randomized; how can that improve the evidence that we have at approval and might help fill some of

those evidentiary gaps in terms of uses of the drug; how can we use purely observational data; is it completely out; is it possible that some of this data could support regulatory decisions; can it supplement clinical trials; how would you do that; how would you build -- how would you use registry information in regulatory decisions? I don't think we can say none of this should be used at all by the Agency, but I think what we need to do is seriously consider a program that might look at what are potential uses of this; what are appropriate uses of these kinds of data; and what are some new methods that might help make these data more useful for the Agency because there are critical evidentiary gaps at the point of approval. Oftentimes physicians are making decisions and patients are making decisions about drugs for a particular patient that wasn't necessarily represented in clinical trials. So we need to think about how we might bring more evidence to the Agency in making the approvals.

And then finally, in this very quick

last point is moving beyond PDUFA V, this idea of improving innovation measurement. Significant challenges exist in compiling data on the actual drug approval process itself. For example, policy analysts might say, oh, you know, this year we had 41 NMEs approved, last year we had less than that; therefore, we're doing better. We might be but what might also be important to understand is are those products, on average, addressing unmet need. Are they really addressing and bringing new innovation to our healthcare system?

Simple questions like do biomarker development and approval programs, biomarker qualifications, does that actually result in better products coming to market or products coming to market quicker? Precompetitive consortia, are they having an impact on the process themselves? And some of these questions are easy to state but they're hard to measure because we don't have consistently collected data on things as simple as IND dates; what was the date that a product received its IND approval;

what was the actual date the product was approved. That might seem easy to analyze but it's actually really hard to collect those data consistently. You have to go back to Federal Register notices. You have to go back to clincaltrials.gov which is spotty. And PDUFA VI might create an opportunity to -- for the Agency and drug sponsors to collaborate on prospectively collecting some data about the drug development process, what were the dates at each stage, what were the endpoints used, were biomarkers used, other kinds of things that we might collect prospectively. And why would we do that? Because that would help policy analysts. It would help the Agency and it will help other researchers better understand what is really impacting the drug development process; what actually results in a more efficient program; what actually results in getting products on the market that are more innovative.

MS. TOIGO: I'm sorry, but we're going to have to move on.

MR. DANIEL: And so -- and that actually

was my last point so thank you. Thank you very much.

MS. TOIGO: Thank you very much.

(Applause.)

MS. TOIGO: Okay. Our next speaker is Daniel Carpenter.

MR. CARPENTER: Thank you very much for having me. I'm going to try to be quick, at least because the time that I take is not available to my co-presenter, Dr. Kesselheim. He and I are sharing a cab back and I have a feeling if I go a little too long, he's going to take it out on me on the fare.

So just as a general background, I'm going to focus very specifically on two issues, the first of which is the filing review, the extra 60 days that Commissioner Mullin told you about earlier today and -- sorry, not Commissioner -- Dr. Mullin -- sorry. PDUFA 2012, PDUFA V requires that the FDA complete a filing review within 60 days from the NDA filed. And that's sort of associated with a set of concerns that arose in

the years before 2012 on the dynamics of FDA approval. One, as people here will undoubtedly know, the completeness of NDA filing is not always the fault of the company, often a matter of communication between the FDA and the sponsor.

Second, some work that I've done with others and that others have done on the deadline piling of approvals, the great increase in the basically approvals that occurred or decisions that occurred right on the PDUFA date. And just to give you a review of that, we found that for PDUFA goal dates in the weeks before, about a 12-fold increase in the odds of an approval on those dates relative to the pre- PDUFA period, nothing necessarily wrong with that and nothing necessarily wrong with what I'm about to show you, which is those at deadline approvals were, compared to very quick approvals or slower approvals, much more likely to require revision postmarket, seven more times likely the odds of a safety base withdrawal, about three times increased odds of black box warnings or revising

the label, and for every 10 drugs, about 5 additional safety alerts added. Again, this may not be a bad tradeoff to make but it is worth keeping in note as we look at previous PDUFAs.

So, the questions that I have are in light of the review filing experience, number one, are total approval times significantly longer? If so, are they actually 60 days longer or more or less? Do reviews still pile at the deadlines as often?

My review -- my -- just a preview, what I'm going to tell you today, there is no evidence of any statistically longer approval times as a result of the filing extension. Are they 60 days longer? No; on average, they're zero. And they pile at the deadlines as we would expect many administrative processes to do but far less likely, in fact, the frequency of very quick approvals as we see with the breakthrough category h as increased in recent years.

So, just to give you a sense here, what we're going to do is I'm going to show you just

some of the data for new molecular entity and BLA approval times. We're going to focus on all cycles but we'll control for those cases where it's a first cycle approval. It's a sample of 152 NMEs submitted between 2001 which is to say in the year-and-a-half-two years right before PDUFA V took effect and the two years- three years afterwards, you can see again -- although this is affected by outliers in part -- that the mean length for time prior to PDUFA V has, in fact, fallen but again, that's somewhat due to outliers. Here is a density plot of the approval times for these NMEs and BLAs. In the "pink" is what happened for PDUFA V and in "blue" is the several years -- the two years before PDUFA V which was our experience with the end of PDUFA IV.

We see a general contraction in this distribution which I will show you alternatively here. And I'm hopeful that these are -- oh, you have black and white graphics, don't you. Okay. Well, right about here is the distinction between

PDUFA IV and PDUFA V and several things are happening. First, you're seeing a general contraction in the distribution where these really long multi-cycle approvals aren't happening as often. That's what other people have noted today.

Second, you'll see these lines here which correspond to the FDA actually, in the case of priority drugs and in the case of standard drugs, CDER is, in many cases, taking the extra 60 days. However, keep this in mind. You're seeing a lot more very rapid approvals and for those of you thinking statistically, this cannot be explained by censoring the data. I can get to that later; all right?

So, if we look at another basic analysis and we say what has happened -- what is the effect controlling for cycles, controlling for priority approvals, of PDUFA '12 OR PDUFA 2012, PDUFA V, on overall approval times, the basic answer is zero. There is a statistical decline that is purely

descriptive but the extra 60 days has not added overall time on the mean.

What is has done perhaps is to have led to an increase in quicker review s. I can't say this is causal but if we take a look at standard and/or priority and non-priority NMEs and BLAs and we just code for one fact, whether they were approved more than 30 days ahead of the goal date, right, which is by definition, by the way, first cycle approval, we see the odds for PDUFA 2012 compared to the last two years of PDUFA IV about 2-1/2 times increase in the odds of a very quick approval defined that way. If we control for review cycles, it actually goes up. So actually, if we control for the facts that many of these are non or first cycle reviews, we actually get an odds ratio of about three. In other words, in many cases, more time -- I don't want to say leads to; that's a little bit misleading on my part -- it's associated with not necessarily causal of these quicker reviews.

So, to conclude, the experience is early

obviously. We don't have data. We don't have data on safety and quality outcomes of these drugs. The FDA, under the review filing provisions of PDUFA V does, in many cases, take the extra 60 days. However, there is no statistically significant difference in review time pre-PDUFA V/post-PDUFA V. There actually appears to be less piling on the deadlines, especially for the priority applications and there is actually a statistically detectable increase, again, even with small samples in very quick -- again, what I'm calling very quick -- one-month or before the deadline approvals.

One last point and then I'll conclude and turn it over to my co-collaborator. I want to applaud the recent data-sharing arrangements that people have talked about including BIO and PhRMA's PDUFA tracking tool. As much as possible, I would suggest -- and this is a message, in part, to our industry colleagues, I think as much as is possible, this data should be made public. It would create a vast public good for all of us to

better understand the process, including for those NMEs and BLAs that do not get approved, and I think vast amounts can be published indeed by FDA in consultation with PhRMA and BIO without violating the commercial secrecy or proprietary exemptions to the Freedom of Information Act. Of course, the industry is already sharing this data anyway, which leads you to believe that those are not immense issues.

All of the data that I used today is available at the FDA projects website at Harvard's dataverse and these are my disclosures. Thank you.

MS. TOIGO: Thank you. I'm glad you put some extra money in your wallet. Dr. Kesselheim.

DR. KESSELHEIM: All right. So thanks. So my name is Aaron Kesselheim and I run the program on regulation, therapeutics and law at Harvard Medical School, and here are my disclosures. I have no financial relationship to disclose.

And what I want to do in my remaining

three or four minutes is talk to your about two studies that we've done looking at the effect of PDUFA designations, specifically the breakthrough therapy designation that was started in 2012. The breakthrough therapy designation is intended to attach to new products treating serious life-threatening diseases for which preliminary clinical evidence of substantial improvement over existing therapies, although that evidence can be very preliminary including effects on a pharmacodynamic biomarker that doesn't meet criteria. It does not change an approval standard but is intended to designate -- to expedite development and review and is, in fact, the fifth formal effort that is intended to shorten or has the effect of shortening the clinical trial or FDA review process on top of the orphan Drug Act, the fast track system, and the accelerated approval and priority review systems that were formalized in the first PDUFA back in 1992.

So we did a study looking at trends and the sue of these programs over the last three

decades approximately, building a database of 774 prescription therapeutics of which one-third were designated by the FDA as first-in-class agents and looked at the application of these accelerated designations to these products. And what we find is that we see a statistically significant increase over time in the mean number of designations granted from the beginning of about .6 or about .7 to over 1.3 designations per drug and an increase -- also a statistically significant increase in the proportion of newly approved therapeutics that are granted at least one of these four designations.

One of the things you could say is well, maybe what's happening is that there are just more very important drugs being produced. So then what we did was we separated this database into first-in-class and non-first-in-class drugs, and what you find is that there is a similar increase in the mean number of designations but that in general, the increase in the number of new designations overall is being driven by these

designations being added to drugs that are not first-in-class and therefore much less likely to be innovative or transformative products.

Why is this important from a public health point of view? Because of the efficacy and safety concerns that come from accelerating development and review of new drugs. There are studies showing that drugs receiving fast reviews have higher risks of adverse reactions. We did a study comparing a sample of orphan cancer drugs versus non-orphan cancer drugs. Many of the orphan drugs were approved on the basis of far less -- far more limited data and showed a 72 percent greater odds of serious adverse events and a non-statistically significant increase in the odds of death.

And of course, the -- I just wanted to point out very quickly that our history is riddled with surrogates thought by physicians to be useful that ended up being ultimately related to mortality and morbidity as bases for their clinical use.

And so then we ask is history repeating itself in the context of the breakthrough therapy designation given the fact that in the first two years, 68 drugs, and now over 80 drugs were designated as breakthrough therapies. Even the senator who initially introduced legislation has been quoted as saying that "rollout was faster than he expected." Here are some of the drugs that were approved on the basis of breakthrough designation. I think it's conceivable that four new breakthroughs occurred in the context of CLL in the last two years but I'm skeptical that all of these drugs are truly breakthroughs.

But nevertheless, the second study that I want to tell you is this -- is what the implications are of giving a product a breakthrough designation and in order to study this, we did a randomized national sample of over 1,000 board certified internists and internal medicine specialists. We got 718 respondents for a 62 percent response rate and asked them four questions. The first three questions are what's

the minimum level of evidence that the FDA requires in order to gather -- to label a drug as breakthrough and gave them three choices: strong, randomized trial evidence, preliminary evidence or very preliminary. And then we asked them two questions. When FDA calls a drug a breakthrough, does that mean that there's high-quality evidence that the drug is more effective than currently approved treatment and safer than currently approved treatments and asked them "yes" or "no" for reach.

So what we found is that over half of physicians think that when a drug is labeled as breakthrough therapy that there is strong randomized data suggesting that there is -- that the drug works, whereas that is obviously not the case based on the requirements. We found that only a quarter of physicians correctly identified that there does not need to be high-quality evidence that a breakthrough therapy is more effective than currently approved treatments, although 74 percent did agree -- did correctly

identify that high-quality breakthrough drugs do not need to be safer than currently approved (inaudible) So then our final question is we asked them imagine your patient has a serious medical condition for which there has been no effective treatment, the FDA approved two drugs, both are oral tablets, blah- blah-blah, which would you choose first, Axabex, a hypothetical drug, and FDA designated breakthrough drug, or Zykanta, a drug with early promising study results but which has not been show to improve survival or disease-related symptoms, which is the definition of a breakthrough drug. Obviously, since these two things are interchangeable, we would expect about 50/50. What do you think we saw? Ninety-four percent of physicians agreed that they would choose Axabex over Zykanta.

So in conclusion, I think what these data show is over time, an increase and creep of designations towards drugs that may not be truly the most transformative products meeting unmet

medical needs for which these designations are appropriate, that physicians generally misunderstand the meaning of what a breakthrough therapy is.

And so as part of the suggestions of what to do, I think we should think about resisting the urge to create still more expedited designations. We should formally reexamine these programs. There isn't a lot of data out there apart from the data that I'm showing you actually analyzing these programs in any kind of rigorous way, and consider instituting more rigorous qualifications for having drugs qualify for these programs. You know, is the FDA wasting its resources on less innovative or clinically impactful products and what are the risks the patients of these various designations. We should study the implications of these labels on physician prescribing and patient outcomes. And we should also, as others have mentioned, enhance FDA authority, or will mention, I guess, to enhance FDA authority to require postmarket

testing and then to withdraw a drug if it does not meet its goals. Thank you very much.

MS. TOIGO: Thank you, Dr. Kesselheim.

(Applause.)

MS. TOIGO: Okay. Next, we'll hear from Ernst Berndt from MIT.

MR. BERNDT: Thank you. I appreciate the invitation to present here. I'm going to address two issues: who makes this drug and who gets this drug. By who makes this drug, I'm referring to the fact that public access to critical information regarding where a drug is manufactured, whether it's dual sourced, whether it's outsourced to contract manufacturing and so on is critical information for decision-making yet it's not public. And what we've seen, some instances that were difficulties in tracking down shortages. Who gets this drug? The FDA is no longer the sole gatekeeper for access to new meds. Patient groups, providers, insurers are negotiating access to drugs in development and insurers are restraining access once drugs are

approved. Witness, the hepatitis C events.

Let's begin with who gets this drug. Patients, physicians, and payers attitudes and expectations for access to drugs and development are changing. For example, the state's right to try laws that have been passed. The various stakeholders are actively attempting to manage access to marketed but expensive meds such as particularly specialty meds. So this raises the issue of how to coordinate multi- stakeholder interactions to promote accelerated but safe and effective access over the lifetime of a drug.

There are various possible approaches. One we've had at MIT involves hosting pre-competitive scenario design quarter workshops that are discussions with developers, regulators, payers, patients, providers, and academics focused on the exploration of how do you gradually encourage access to the drug. The goal is to obtain broad stakeholder agreement on accelerated access with enhanced post-approval data collection and the monitoring of safety and effectiveness.

One such effort is dubbed "adaptive licensing." There are numerous variants. In March of 2014, the EME announced its adaptive pathways pilot program, invited applications from industry. By December of last year, they had 34 such applications; 6 were accepted for further consideration in what the EU calls its "innovative medicines initiative."

So, what are the to do sort of thoughts we have when reauthorizing PDUFA VI. Consider a mandate for a multi-stakeholder collaboration, not just the developers, regulators, and patient advocacy groups that are emphasized in the 21st Cures Act but also payers, providers, and insurers and that the FDA serve as a home to pre-competitive discussions, research and pilot activities to advance patient access to safe and effective medicines over their lifetime to promote a, sort of in line with the last speaker's comments, post-approval collaborative learning and data generation within a safe haven. Thank you.

MS. TOIGO: Thank you. And our last

speaker is Rena Conti.

MS. CONTI: Good afternoon. It's an honor and a privilege to be here. So I'm going to focus on who makes this drug. While very oversimplified, I like to think of the FDA having purview over both the base ingredients of drug manufacturing but also the fill and finished products of drugs. And within drugs that are fill and finished, we have both generic drugs but also drugs that are enjoying patent protection. Among all of these drug developers, they can make their own base ingredients and/or fill and finished drugs or an outsource those drugs to contract manufacturing organizations.

Now the use of contract manufacturing organizations has actually increased quite substantially over the past decade. We believe this is largely or partially related at least to mergers and acquisitions occurring between generic manufacturers amongst themselves but also between generics and branded manufacturers. We believe the incentives for using contract manufacturers

likely bind differently among branded versus generic drugs. Indeed some work by colleagues at the FDA has recently suggested that brands are much more likely to list CMOs as -- on their GMFs than do generics. And this kind of makes sense from an economic perspective because the incentive to ensure that there is backup facilities when supply interruptions occurs really matter to ensuring the high revenue stream for certain selected branded drugs.

However, as you all know, the U.S. has been subjected to very significant and increasing frequency and also duration of shortages over time. And notably, drugs that are going into short supply are not only generic drugs but also appear to be branded and branded generic drugs. And perhaps most intriguingly, the manufacturers that are reporting these shortages are both traditionally understood contract manufacturers but also branded and generic drugs. This suggests to us that the listing of backup facility among contract manufacturers may not really be the

metric that we need to assess exactly who is making these drugs and which manufacturers have the true capacity to manufacturer these drugs, particularly as one manufacturer runs into supply problems.

Now, what does this have to do with PDUFA? Well, we believe that PDUFA fee schedules both alone and in its interaction with GDUFA fee schedules may enhance the incentives to outsource the production of these drugs. Let me explain briefly how. PDUFA fee schedules are split between annual establishment fees and product fees whereas GDUFA fees are facility- specific. There are no product-specific fees under GDUFA as it exists now. This creates a couple of potentially unintended consequences. First, generic manufacturers do face incentives that are pretty strong to outsource the manufacturing of their drugs to contract manufacturers. Secondly, branded manufacturers have an incentive to act as contract manufacturers both for those generic drugs but also for other branded manufacturers

over time.

While we do not advocate that the PDUFA fee schedule move towards the GDUFA fee schedule, we do believe that kind of more data around the collection but also the ascertainment of whether PDUFA and GDUFA user fees are actually inducing concentration over time is an important piece of information that deserves study by both the FDA and other observers.

At this time, the FDA is the only organization that can actually do this type of assessment. Why? Well, the actual manufacturers of both base ingredients and fill and finish drugs, regardless of whether they're branded or generic, is not public information; it is not available in FOIA requests -- I tried. And, therefore, it is simply an open question that exactly who is manufacturing these drugs at any given point in time.

In previous presentations at the FDA, myself and also Sylvia Bartel have suggested that this lack of transparency, particularly when

shortages occur, clearly harms public health. But I would like to suggest in this presentation that there's this additional implication here which is the lack of information on who makes this drug fundamentally hampers other independent researchers, both academic but other types of stakeholders for assessing what the source of these drugs actually are and counting the actual number of manufacturers and whether, frankly, there's just simply dual source really existing in this market or not. This matters for shortages. This also matters for forecasting supply, what the price of these drugs are, and a variety of other important aspects.

So given this, we suggest two things. The first is that the FDA, in PDUFA reauthorization, should consider making the identification of exactly who is making these drugs and supplying them to the United States public and in the meantime, should also pursue, understandingly that there's give -- there are scarce resources, some examination of the

potential intended and unintended consequences of PDUFA fee schedules for inducing perhaps more concentration than may be socially optimal. Thank you.

MS. TOIGO: Thank you.

(Applause.)

MS. TOIGO: So that concludes our panels. And lessons learned for meeting management, two academics cannot split 10 minutes. They each need to have their own time allocated. At least we were consistent. Okay. So now we'll hear from Dr. Woodcock, some closing remarks. And while Janet is coming up, if our -- the speakers who signed up for the open public session can move to this front row here, Peter Pitts, Stephen Sun, David Schoneker, Paul Brown, and Tiber Sipos -- I may have not got that correct. So if you can sit in this front row so that when we're ready, we can do that in an efficient way. Okay. Dr. Woodcock.

DR. WOODCOCK: Thank you. Well, I'd like to thank everyone for coming to this meeting. It's valuable for us to have input from the public

on this program and its impact and suggestions for the future. Some of the themes that we have heard, both in this meeting and generally, are the importance of the patient's experience in drug development. And we got a toe into this in our last PDUFA and have gotten tremendous from the patient community, so I think that is something we need to continue considering in this next round.

Strengthening exploring additional uses of Sentinel and in general, how to make sure that our postmarket safety programs are robust and respond quickly and can manage postmarket safety evaluations effectively.

And then continue to build on our regulatory science activities which has to do really with the science of drug development and drug evaluation, and there is a tremendous of work to do there and we have only, I think, just looked at the surface of that. So those are very important.

Now, I want to make a few comments on PDUFA so everyone is aware of sort of the

parameters here. PDUFA is a sort of fee for service type of structure that's set up by Congress. And within PDUFA, we do not negotiate nor do we go into policy matters, many of which have been raised, of course, during the course of this meeting. That is separate so if something requires legislation or regulation change or whatever, that's really not what PDUFA is about. It's really about what additional can be done for user fees and how to structure a program that meets the needs of the public, drug developers and so forth effectively with additional -- with these user fees that we have.

So I know every user fee program we have, there is always a tremendous temptation and most of the bills that we've gotten in conjunction with the user fee programs have multiple other policy matters added on to them but these are not a subject of PDUFA itself, and I think people really need to keep that conceptually straight in their minds. We are not in PDUFA offering policy changes in response to user fees. User fee is

strictly a fee for service type of arrangement for services that have been agreed to by Congress that we should perform.

PDUFA has been generally considered successful. We continue to meet or exceed nearly all our application review goals. One of the goals of the program was to have higher first-cycle approval rates. And why is that? Because if we have to do rework over and over again for a drug that is eventually approved, then that is not a good use of anyone's time, and so we need to get the requirements right the first time and make sure that the industry is clear on what they need to submit and what our standards are.

At this time, nearly four-fifths of NMEs or BLAs are approved on the first cycle and so I think that's very good for everyone. Most novel products are receiving, as we heard from some of our speakers, some sort of expedited review. And 2014 was really a good year for novel rare disease approvals with 17 approvals for targeted rare diseases, which is very good news for that

community. And these accomplishments are, in part, made possible by the resources provided by this program.

So the review program that has been discussed a little bit that was authorized in PDUFA V was intended to improve transparency and communication between the review team and the applicants to improve the likelihood of a first cycle review. And so we feel that program is operated as predicted. It has improved communication and transparency and that, I think, is good for everyone because we're able to clear up misunderstandings and so forth and make sure that we've -- that everybody has done what they can during that first review cycle.

Now we have launched under PDUFA V, as I said, the patient-focused drug development initiative. This current initiative has mainly focused on hold in patient-focused drug development meetings and capturing what patients have to say. What we have learned from that is that people with chronic diseases are really the

experts in their disease and what their disease impacts. And so we think there's a tremendous amount to learn from that in drug development but we need new ways. We all recognize, I think mutually, that patient-focused drug development meetings are just kind of the way that we use to figure out what we need to do next and much more needs to be done to collect information from patients in a rigorous and unbiased manner so that we can really elevate the patient's voice in drug development and make that voice central.

FDA has developed and begun to implement -- and this was another agreement under PDUFA V -- a structured benefit-risk framework into our clinical review template. And what does that mean? That's bringing more rigor and clarity and sort of uniformity into our assessment of the benefits, the risks, the residual uncertainty related to a drug product when it's going to get onto the market if we make and approval decision. And also, when we decide not to approve a drug, we can, you know, have a structured explanation of

why the benefits did not seem to exceed the risks or the harms.

We've also -- in PDUFA V, we agreed to improve communication with drug developers using a dedicated liaison team and we have been operating that.

And our regulatory science initiatives have focused on meta analysis, biomarkers, pharmacogenomics, patient-reported outcomes, other endpoint assessment tools and also rare diseases and we've made progress in each of these areas although as I said, there is still a tremendous amount to be done. This comes under the general rubric of translational science, an area that I think has been neglected and I'm very glad that PDUFA has provided some funding and opportunity for us to advance these scientific fields.

Now we see value in further enhancements as sort of our ideas around review program refinements to increase the quality and predictability of drug development and review. Clearly, much of this is in drug development, you

know, because once we get the application, no matter how much time we take to review it, okay, whatever is done is done and whatever data are contained and have been generated are done in the development program. And so that's where the money is, is to make sure that that development program covers the bases, that it evaluates the drug thoroughly and to the extent that is needed for the particular disease condition.

We also would like to enhance financial soundness in the program -- that was alluded to by one of the last speakers -- through evaluating the fee structure and enhancements to the fee structure to make sure they're aligned with public health goals because we don't want to have unintended consequences from fees that we levy and cause disruptions that have negative consequences.

And finally, recruiting and retaining critical staff for new drug review, this is something we continue to struggle with. The Center for Drugs continues to be way below our ceilings for people, and we need the best and the

brightest staff to do these evaluations, and we need to have the tools to recruit them and also to retain them.

So we look forward, really, to the ideas of the pubic and all the stakeholders involved in this program as we go through the process of trying to evaluate what the next program might look like, and we're looking forward, we hope, to a timely reauthorization of this critical program. Thank you very much for coming.

(Applause.)

MS. TOIGO: Thank you, Dr. Woodcock. So we'll now go to the open public comment section of the meeting and we'll start with Peer Pitts. You can come up here.

MR. PITTS: Thank you, Terry. Good afternoon. A few quick comments. I think it's important to applaud that we've moved from the first principle of PDUFA which was predictability of the process to include also facilitating the advancement of regulatory science. Janet mentioned this; others did. It's incredibly

important and this is made possible some crucial things: biomarkers and functional endpoints, risk-benefit, patient-centered drug development which really should be called patient-drive drug development, 21st Century pharmacovigilance, bioequivalence, and quality programs, 21st Century clinical trial development but much more is left to be done, and PDUFA VI must continue this work but it must also help to redefine what success looks like.

As Janet said and it's worth repeating, "What comes next?" Dr. Ostroff this morning asked us to aim for the starts. Bravo. But let's not settle for an easy, clean and comfortable low altitude orbit. "Per aspera ad astra" -- "through hardship to the stars." Nobody said it was going to be easy. We've had FDAAA; we've had FDASIA. Now perhaps it's time for FDAMN, FDA Momentum Now. Thank you.

MS. TOIGO: Thank you, Peter. Next, Stephen Sun from Inventive Health Clinical. I can't read the writing so you'll have to --

MR. SUN: That's okay. Okay, great. I'm going to take up all the minutes that I can get here.

MS. TOIGO: You have five.

MR. SUN: Got it. I'm going to take them, all five. Thank you for the opportunity to speak. So my name is Stephen Sun. I'm the Chief Medical Officer for Quality Risk Management Group for Inventive Health Clinical. Inventive Health Clinical is a global contract research organization for pharmaceutical companies. However, today I'm speaking as an individual stakeholder. Historically, I've worked as an industry physician at a generic, brand and OTC company and also as a former medical officer in CDER's Division of Risk Management in the Controlled Substances staff. So there are lessons learned to be shared on both sides.

Here are three suggestions for you to consider as you're planning for PDUFA V which I believe are risk-based, high yield, public health initiatives the FDA could implement. Number one,

requiring systematic risk assessment for clinical studies and approved products. Number two, initiating a visual medical language for benefit-risk communication. Number three, incorporating location and time for adverse event case reporting.

So here's the first recommendation. Wouldn't it be nice if a fireman who was going to rush into a burning building has a blueprint in hand before running in? Every FDA reviewer is like a fireman trying to address risks ahead of time but if not, they still run in and try to put the fire out. A well- conceived map of risks allows a review er to put their finger on where the trouble spot is with surgical precision and still have the ability to address the risks ahead of time or navigate through an inferno. There is a REMS for high-risk approved products but everyone knows that only scratches the surface of mitigating all the risks and medication errors and adverse events that occur.

FDA also released a risk-based

monitoring guidance for a clinical study risk database for regulators and sponsors to realize data integrity and subject safety being better managed if you focus your fixed resources on the highest risks. Do you know in 21st Century Cures bill, minimal risk is mentioned and then risk is referenced 62 times in the document. Questions for a reviewer are often did we get the risks right; are these all the risks; are there other risks. So here we're recommending a systematic risk assessment using tools such as failure modes and effects analysis or FMEA for clinical study in an approved product, gives you a comprehensive risk blueprint if a fire is burning.

FMEA is an engineering standard tool for proactively identifying ranking and managing risks that's used and recognized already by CDER in manufacturing and in CDRH and medical devices based on FDA's 2006 ICHQ-9 guidance and quality risk management. FDA lives in a world of a fixed resources where FDA cannot be everywhere and a risk-based approach of going where the risks are

is the new default. As such, systematic risk assessment for clinical study and an improved product used during the medication review process would give you the blueprint to show you where all the risks are located and how to mitigate them prospectively. Sponsors can say "yes, we recognize all the risks of our clinical study and our marketed product and we want to proceed," and FDA says, "yes, we recognize all the risks you have descried and all the benefits still outweigh the risks and you can proceed." So consider making SRA as a requirement for all clinical studies as part of an application for product approval.

So for my last two minutes, for my second recommendation, next time you're on a flight, check the seat pocket in front of you and read the colorful panel foldout instructions of how to exit a plan in 60 seconds with a lift jacket onto a floating raft using only a handful of visual instructions with a cartoon brochure. The airline industry is able to communicate and

provide such clear instructions to such a diversity of cultural and educational backgrounds while we struggle here in the pharmaceutical field how to explain putting a pill in your mouth for better health. In a current state, we recognize text-heavy, English-only medication guides have minimal effectiveness so we should do something different. Visual communications are a very efficient form of risk communication. Think of this as you get to your first traffic light after today's meeting. And my 76- year-old partially English-speaking Taiwanese mother will tell you what "red," "yellow," "green" means and any of the traffic signs nearby.

My recommendation here is that a visual medical language or VML standard similar to a (inaudible) for adverse event reporting be initiated in PDUFA VI so that we can explain the benefits and risks of medical therapy regardless of cultural, education, or socio-economic backgrounds. In New Jersey, I've had to take cultural literacy tests as part of a medical re-

licensure so this is in line with medical practices at a state level. CDRH has begun to explore it. CDER should also.

So if you want risk communication to be communicated faster, cheaper, and better in our mobile device world with shrinking attention spans, a visual medical language incorporated into labels, medication guides, product packages will deliver your information faster, cheaper and better. Visuals are the executive summary that reduces the variability and interpretation of the textual language. Visuals are the global currency of information exchange among countries. Visuals will also be able allow us to move drug regulation into mobile and real-time information centric and global 21st century.

My third recommendation, the FDA should prepare for a mobile and real-time two-way information society and have a comprehensive mobile information platform strategy. Ninety-five percent of the people in the room have a mobile phone and the rest of you probably left it at

home. As a start, when we manage safety signals, the error of reporting adverse events should move from the standard four-element criteria of patient, event, product, and reporter to now also include two critical elements which are location and time. This is somewhat possible with today's technology but the future of drug regulation for safety surveillance would benefit greatly since we know that location will reflect culture, population, and local environments while time of an adverse event will acknowledge what was the state of information that was known at the time of the event.

GIS is today's technology to address today's mobile society. The Office of Crisis Communication already uses it. So again, the third recommendation is that your reporting should add location and time to the current four element criteria. Consider that if you increase the number of criteria for a qualified AE case report, it may reduce the regulatory and sponsor volume of case reporting without compromising patient safety

and you have more actionable information. When to start? The time is today and the location is Silver Spring.

So thank you again for this opportunity and its' always a pleasure to help advance the public health mission of the FDA.

MS. TOIGO: Thank you, Stephen.

(Applause.)

MS. TOIGO: Tibor Sipos. You'll correct me on the proper --

MR. SIPOS: That's correct. Hello, everybody. My name is Tibor Sipos. I'm the President and Chief Scientific Office of Digestive Care, a small but innovative company that is working on drug development in the cystic fibrosis area and other orphan drug categories. I would like to thank the organizers for giving me this opportunity to comment about an adverse effects of the interpretation of the small section of the PDUFA for small companies. At the conclusion of my comments, I will offer suggestion for minor changes.

Whether a U.S. patent -- okay, before -- to -- first of all, to prevent PDUFA fees from strangling innovative small companies, Congress passed a fee waiver provision. FDA's policy for implementing that provision is set forth in a 2011 guidance. The guidance tells how FDA decides if a small company's product is innovative enough for a waiver. Whether the U.S. patent has been obtained is not one of the criteria being considered in the guidance. The guidance speaks of breakthroughs, superiority, uniqueness, new molecular entities, or whether the manufacturer has received federal grants. New molecular entities represent a very small proportion of first product for small companies because of the large amounts of resources necessary to develop testing.

But I can assure that it takes a lot of innovation to develop a new dosage for, for example, for pediatric dosages, or a new formulation with improved bioavailability and a greater stability to a previously approved drugs. But this kind of innovation is not judged being

innovative enough to get a PDUFA fee waiver for small companies, and that is a policy that has adverse consequences that has (inaudible) opposite results that are obviously not well-appreciated.

The drug industry is concentrating largely to mergers and acquisitions. You don't have to be an economist to know that supplier concentration results in higher prices to consumers. Small businesses seeking PDUFA waivers for variations of previously approved products or potential new market entrance, the strict innovation requirements for waiver discourages them from developing products that compete with existing lesser effective products. That policy ends up supporting again higher drug prices for consumers. Actually, it's even worse than that.

Granting waivers to small companies don't affect the total fees FDA receives. The cost of waivers is recovered in the fees assessed in the next fiscal year, so waivers are basically revenue neutral for FDA. But by denying small entrant companies waivers, FDA is basically taking

money from new competitors and giving it to current market participants in the form of lower PDUFA fees.

Here are my suggestions for improving PDUFA. I simply recommend that the added innovation requirements for small businesses be re-examined or eliminated completely. Number two, I encourage FDA to immediately simplify the PDUFA fee waivers process by establishing an automatic fee waiver exemption for small pharmaceutical and biotechnology companies that have less than 20 million in total annual gross revenue based on annual IRS tax filing documents. The waiver qualification would be automatically renewed each year for companies that continue to meet the 20 million gross revenue limit. Refusing to grant a waiver to small companies just makes sick people pay more for their medication.

Thank you for this opportunity to comment on the adverse effects of the current interpretation of the PDUFA fee waiver provision for small companies.

(Applause.)

MS. TOIGO: Thank you. Our next speaker is David Schoneker from IPEC-Americas

MR. SCHONEKER: Thank you. My name is Dave Schoneker and I'm here representing International Pharmaceutical Excipients Council of the Americas today. IPEC-Americas is an industry association that develops, implements, and promotes global use of appropriate safety, quality, and functionality standards for pharmaceutical excipients, otherwise known as inactive ingredients. IPEC-Americas is an FDA-defined -- excuse me -- thank you for the opportunity to speak regarding a very important issue involving the need for an FDA novel excipients safety review and qualification process which could be performed independently from a specific new drug application. This addresses FDA's third question about new areas for PDUFA to be involved in.

I think Americas and FDA define a novel excipient as a material or a composition that has

not been previously used in an approved drug product in the U.S. The FDA's own definition of new or novel excipients in guidance documents would include various types of novel excipients, everything such as a higher level of use of an existing excipient which is a fairly simple situation all the way to an NCE or a type of excipient that provides unique benefits.

The level of safety assessment needed increases based on the type of novel excipient. The degree of newness for different types of novel excipients will influence the amount of safety data required to complete an appropriate assessment. Novel excipients can enhance pharmaceutical safety and efficacy and may present opportunities for accelerating new therapeutic mechanisms, for example, by enabling low solubility candidates to create valuable and proved drug products for patients. Novel excipients can also assist in the development and use of advanced manufacturing technologies such as continuous manufacturing. They can increase the

robustness and efficiency of traditional processing and they can play an important role in addressing patient needs by extending uses and presentations for existing medicines, for example, in pediatric medicines.

Although novel excipients have many potential benefits, the regulatory review process for excipients is viewed as posing an impediment to the use in pharmaceuticals. The FDA's current approval mechanisms do not include a process for evaluating the safety of novel excipients on their own. Rather excipients are evaluated as part of the drug product. As a result, pharmaceutical companies face uncertainty in the use of excipients in a drug product due not to the safety or efficacy of the drug but to the acceptability of the excipient to regulatory authorities. Without assurance that an excipient will be found acceptable by regulators and that they're providing appropriate safety information in a drug application, the risk of using a novel excipient typically deters pharmaceutical from incorporating

them into their drug products unless they have no alternatives thereby limiting innovation and benefits to patients.

This leads to the development of drug products and/or manufacturing processes that may be, quote, good enough but probably not optimum. This is not conducive to quality by design.

Adoption of a new review process by FDA that provides for stand-alone, independent review and qualification of excipients would inspire innovation within the excipient industry and encourage pharmaceutical companies to use novel excipients for improved formulations resulting in important benefits for patients. IPEC-Americas would like to work with FDA to develop a regulatory process for improving development and adoption of novel excipients. This would include an independent safety assessment of novel excipients outside of a drug application where the sponsor could indicate the intended types of use and levels.

IPEC-Americas is not looking for an

approval of the excipient but rather a way to have the safety of the excipient evaluated and qualified for potential use in a particular round of administration exposure level. Coverage under a PDUFA-type user fee system could provide resources to FDA to perform these independent safety assessments or qualifications. This qualification process could result in the publication of a list of excipients that could be considered qualified for specific intended uses and levels in pharmaceutical products.

IPEC-Americas is working with the IQ Consortium, which is a group made up of primarily the major innovator drug manufacturers to determine how best this can be done. We're actually reviewing the biomarker qualification process that was alluded to earlier to use that as a possible model for what we could possibly do with novel excipients.

We wanted to bring up this request in this PDUFA reauthorization public meeting because we think that the development of such a process as

I've outlined would enhance the development and regulatory processes for innovator drugs under PDUFA. IPEC- Americas recognizes that a unique type of user fee system would need to be developed for the independent novel excipient safety review process which would probably somewhat be different than the existing PDUFA user fee model.

We would like the opportunity to continue discussions with FDA pertaining to possible approaches to create an improved pathway for review and acceptance of novel excipients based on defined criteria and mechanisms by which such a process could be formally recognized. We believe that this will enhance innovation throughout the pharmaceutical industry and encourage excipient manufacturers to develop new and innovative excipients that can solve pharmaceutical formulation problems.

IPEC-Americas will be submitting written comments to the document before the August 15th deadline which will include more details of our proposal. Thank you for the opportunity to

provide these comments today.

MS. TOIGO: Thank you, David.

(Applause.)

MS. TOIGO: And our last speaker for today is Paul Brown from the National Center for Health Resources.

MR. BROWN: Good afternoon. Thank you for the opportunity to speak. I'm Paul Brown. I'm government relations Manager with the National Center for Health Research where our think tank scrutinizes scientific and medical data and provides objective health information to patients, providers, and policy makers. We receive no funding from the pharmaceutical industry and so I have no financial conflicts of interest.

The National Center for Health Research has tremendous respect for the Food and Drug Administration and is committed to ensuring that the Agency has the resources it needs to keep our medical products. That's why our President, Dr. Diana Zuckerman is on the Alliance for a Stronger FDA.

In the real world, in the ideal world, Congress would provide generous appropriations to the FDA so it can meet its enormous public health mission. But since we live in a less than ideal world, user fees are necessary for the FDA to do its job. It is important to note, however, that the American taxpayer is FDA's most important customer and taxpayers still pay most of the FDA's bills. User fees do not give companies the right to tell the FDA how to do its job.

We agree with the FDA that its job is protecting the public health by ensuring the safety, effectiveness, and security of medical products. Unfortunately, in the last few years, the focus has been too much on speed and not enough on safety or effectiveness. That seems to be the result of PDUFA and it is not acceptable. We know that patients who are dealing with a life-threatening illness are more likely to accept higher risk than consumers facing low to moderate illnesses. However we hear from patients who are devastated and angry when they discover that the

FDA-approved drug that they used has harmed their health or killed a loved one. Dr. Rita Redberg, in a recent JAMA internal medicine article noted that too many cancer drugs are being approved quickly and later found to be ineffective. She concludes, quote, in a rush to find new effective treatments, we should not harm patients with ineffective toxic ones.

One of the questions for this meeting is the overall performance of PDUFA V and our center agrees with the National Consumer League that patients and consumers deserve a drug approval process that provides timely access to safe and effective drugs while reducing exposure to harmful drugs. But PDUFA V focused too much on industry's goal of reducing perceived barriers to new drug approvals rather than protecting and promoting the health of patients.

In response to industry and Congressional pressure, the FDA has been moving its standards of evidence from premarket review to postmarket studies. This is unfair to patients for

the simple reason that companies have no incentive to complete postmarket studies in a timely manner. And patients' health and lives are at stake as cancer drugs and other expensive drugs based on surrogate endpoints don't always lead to overall survival.

As the National Consumer League mentioned, the FDA is meeting most of its performance goals regarding speed and the pharmaceutical industry has many options to speed new drugs to the market. Last year over 60 percent of approved drugs were approved using expedited review or orphan drug status. And Dr. Redberg said, "This has reduced the evidence standards for safety and effectiveness."

Regarding FDA PDUFA VI goals, they must include safety and efficacy performance goals and those goals should include diversity in clinical trials and study samples and study samples that are large enough to conduct meaningful subgroup analysis. This will ensure that patients and physicians can make informed decisions about which

patients are most likely to benefit from which treatment such as women, men, African Americans, Hispanics, Whites, and people over 65.

We agree with the National Consumer League that PDUFA VI should improve the monitoring and enforcement of direct-to-consumer advertising. User fees could improve the public health if used to enhance the Agency's, the FDA's regulation of direct- to-consumer ads.

Regarding Sentinel and off-label prescribing, about 20 percent of prescriptions are off-label use but little research has been done to determine if the impact on patient's health -- that impact on patient health. Sentinel data should be used to determine the possible risk and benefits of off-label drug use, and PDUFA VI user fees should be used to help the FDA do these analyses.

In conclusion, in today's budgetary climate, user fees are necessary and if the 21st Century Cures Act is signed into law, FDA's responsibilities will grow much faster than its

funding. The National Center for Health Research will continue to urge Congress to increase funding to the FDA and that user fees be increased and used to support performance goals that improve the quality of medical products, not just the speed of FDA review. PDUFA VI user fees must be increased to help enhance the quality of FDA's review process before approval and post market. If not, patients will be exposed to drugs based on preliminary data that is too often overly optimistic. Thank you for the opportunity.

MS. TOIGO: Thank you, Paul.

(Applause.)

MS. TOIGO: And that concludes the meeting for today. I want to thank our presenters, especially those working with me to make sure that we stayed within our time. If there were things that you had wanted to say and didn't' get an opportunity to do so, I encourage you to submit them to the docket.

I want to thank our audience who took the time to come and participate and for those who

want to continue to participate in the process, the Federal Register notice should publish within the next week and give you the criteria for doing so.

And finally, to thank the folks in Theresa's office who put together this meeting, Josh Barton, Graham Thompson, Ashley McRea, and Meghana Chalasani. So they helped ensure that we had a good meeting. And thank you all for coming and for those who are going to continue in the process, we'll see you at the next PDUFA meeting.

(Whereupon, at 2:03 p.m, the aforementioned meeting was adjourned.)

CERTIFICATE OF NOTARY PUBLIC

I, NATASHA THOMAS, the officer before whom the foregoing proceeding was taken, do hereby certify that the proceedings were recorded by me and thereafter reduced to typewriting under my direction; that said proceedings are a true and accurate record to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

_____
NATASHA THOMAS
Notary Public in and for the
State of Maryland

CERTIFICATE OF TRANSCRIBER

I, LUCY TURNBULL, do hereby certify that this transcript was prepared from audio to the best of my ability.

I am neither counsel for, related to, nor employed by any of the parties to this action, nor financially or otherwise interested in the outcome of this action.

_____
LUCY TURNBULL
Transcriptionist

P

Q

