FOOD AND DRUG ADMINISTRATION (FDA)

PUBLIC MEETING ON

PRESCRIPTION DRUG USER FEE ACT

(PDUFA) REAUTHORIZATION

Monday, August 15, 2016

Food and Drug Administration

White Oak Campus

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

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

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P R O C E E D I N G S

Welcome

MS. VAIDYA: Good morning, everyone, and welcome to the Public Meeting on the Reauthorization of the Prescription Drug User Fee Act. My name is Pujita Vaidya, from the Office of Strategic Programs and the Center for Drug Evaluation and Research. And I'll be your moderator for today.

So as you all know, today's meeting is an important step in the public process described in the statute to provide an opportunity for stakeholders to provide their views on the recommendations for the reauthorization of PDUFA.

I do want to mention, in addition to today's meeting, a docket will remain open for 1 week until August 22, to which the public may submit comments regarding the recommendations for PDUFA reauthorization.

We do have a full agenda today, so I'm going to get started.

First we'll have Dr. Janet Woodcock, Director the Center for Drug Evaluation and Research,

will get us started this morning with opening remarks, followed by Theresa Mullin, Director of Office of Strategic Programs in CDER, will provide a presentation on PDUFA background and the reauthorization process.

We will then have panels focused on recommendations on specific topics. For each panel, FDA will first provide an overview on the recommendations, and then a panel of stakeholders will have an opportunity to provide their views on the recommendations of those topics.

The panel topics will be as follows: Panel 1 will be on "Pre-Market Review and," of course, "Post-Market safety"; Panel 2, on "Regulatory Decision Tools"; finally, Panel 3, on "Administrative Enhancements: Hiring, IT, and Financial."

Following the panels, we will provide time for public comments. If you wish to sign up to speak during the open public comment period, please do so at the registration table during the break.

A few brief housekeeping items. We will have a 15-minute break around 10:20 and then an hour

lunch break at 11:25. There are food and beverages available for purchase at the kiosk outside of the room in the lobby, and you are welcome to pre-order during the break to avoid lines during lunch.

Bathrooms are down the hallway in the lobby to the left.

And the WiFi password can be found at the front desk in the lobby.

Now I will turn it over to Dr. Janet Woodcock for opening remarks.

Opening Remarks

DR. WOODCOCK: Thanks very much. Good morning, everyone. Thank you all for coming. Today's meeting is really a critical step in the process that was codified by Congress in statute for public input and transparency to reauthorize PDUFA. As all of you are aware, I think, PDUFA is a critical program that's designed to provide FDA with the resources needed to support the New Drug Review Program.

We take the PDUFA commitments very seriously, and we've had considerable success in meeting our commitments over the years.

PDUFA has really evolved significantly since originally enacted in 1992. I was there for the enactment, and I can tell you it's a whole new world. The 5-year reauthorization cycle that we have has provided all of us collectively an opportunity to refine, enhance, and really move the program along, evolve the program.

The well-defined process that we now have builds an opportunity for stakeholder consultation and comment, which includes today's meeting. So PDUFA is really intended to meet the needs of the various stakeholders in the process; and the public, patients, prescriber community, scientific community, are really important stakeholders.

We're very pleased to have an opportunity today to discuss the PDUFA VI recommendations. The recommendations represent a strong and comprehensive set of enhancements and refinements to the PDUFA program.

And briefly you will hear in more detail from Dr. Mullin, but briefly, some of the highlights include enhancing the science of patient input into

regulatory decision-making through a process that will bridge from our very successful PDUFA V Patient-Focused Drug Development meetings that are still ongoing and have proven really very successful in focusing the patient community on how to make their needs known and met within the regulatory process.

And we hope in PDUFA VI to evolve fit-for-purpose tools that will enable patient groups, other stakeholders, the FDA, to collect meaningful patient input on what really matters to them as far as drug therapeutics so that we understand and regulators are applying a benefit-risk calculus that really reflects the position of the patients, what burden of disease means to patients, what relief they are seeking, what different adverse events mean to them, and so forth.

And this is a great opportunity I think in the next 5 years, and there is a lot of enthusiasm, and we are looking forward to your comments.

There will be significant expansion of the Sentinel network and integration of the system into pharmacovigilance activities, as a routine part of pharmacovigilance will be proposed in this round of

PDUFA.

I think this will continue to improve overall drug safety and our understanding of the performance of new drugs once they get out into the market.

Sentinel is really pointed to as a sort of landmark in using electronic health data in a very large-scale way, but we need to really institution-alize that, integrate it into our drug safety activities, and really learn how, in every instance possible, we can rest as much information from the electronic health record and claims data as possible to enhance drug safety. So those are some of the things that we'll be working on in the next 5 years.

Resources for the Breakthrough Therapy Program. Breakthrough therapies have proven to be very popular and get a great deal of attention from the patients and from the press and from the community, and we understand from the industry point of view that this program is also beneficial. It wasn't really fully resourced when it was put into statute, so this will be an opportunity to put

additional resources against it.

A process to begin to explore how real-world evidence can be utilized in regulatory decision-making. Now, Sentinel is the post-market utilization of electronic data out there. The question is, Can it be used to some greater extent in, say, pre-market decisions, particularly those supplemental uses of drugs? And can we understand more about how drugs are used and what their effects are from this data?

I think everyone agrees that, yes, we can. The question is, How do we do it and how do we build on this in a logical and defensible manner over the next 5 years?

Commitments to enhanced administrative functions that support the PDUFA program. I think this will be the third panel today, including enhancements to FDA's internal hiring and retention efforts. We really continue to struggle with hiring and retaining the best and the brightest, and that's who we need to review this cutting-edge science that's coming in our doors every day. And so hopefully these enhancements will help us do that.

And then continued refinements to review process and procedures. PDUFA was originally a process and procedure type of arrangement, so we have more refinements that are being proposed to the NME review program, that's actually been very successful from PDUFA V, meeting management goals, and process for the review of PDUFA-led combo products, drug-device combos that are primarily drug mechanism of action.

This is probably the future as far as precision medicine, is the use of multiple diagnostics along with a new therapeutic. And so the question is, How do all those get reviewed together in a timely manner and are made available to the public?

So all these PDUFA programs have been very successful. We continue to want to make sure that they serve the needs of the public, the public stakeholders, particularly the patients, who are relying upon our scientific review, the prescribers, the scientific community, and the public at large.

And so we look forward to your input, and we also look forward to timely reauthorization of this

critical program.

Thank you very much.

Theresa.

(Applause.)

MS. VAIDYA: Thank you, Dr. Woodcock. Now we'll move into the next session. So I would like to call Dr. Theresa Mullin to the podium to talk about the PDUFA background and the reauthorization process.

PDUFA Background and Reauthorization Process

DR. MULLIN: Okay. Good morning, and thanks for joining us. And it looks like the room was just the right size for the number of people we've had, and fortunately this is the most that we could get of the great room today, so I'm glad it was a big enough size. And welcome to those on the webcast as well. I'm Theresa Mullin, as Pujita said.

And many people in the audience look like you've joined us before in these PDUFA meetings, so I'm not going to give you the full-blown PDUFA 101 because I know you don't need it, but we will talk a little bit and just review for a moment the basic construct of the user fee program and what

distinguishes a user fee from other kinds of funding that we get.

And this is from the guidance that we receive from the Office of Management and Budget. And these funds, and particularly in PDUFA, it's laid out quite clearly in statute, and has been since the beginning of the program, but these are going to be added to our non-fee funds, and they're intended to increase our staffing and other systems and our ability to conduct the review process, and so it allows us to have a more efficient and predictable process.

And because it's a fee, it's really intended to benefit directly to the fee payers and benefit them in a way that exceeds the benefit to the general public, that's actually as we get the guidance from Office of Management and Budget, that it's supposed to do that.

So the user fee discussions that we've had with industry, and we've been able to meet with our public stakeholders throughout that process and get the benefit of their views and preferences and

thoughts about performance enhancements as well, but we focus these discussions on desired enhancements to the activities that are part of that process of human drug review.

And so when we have these conversations, it typically goes like, "Well, what would be enhancements that FDA would like to see?" And then industry tells us what enhancements would they be interested in. We've done evaluations for the previous 3 to 5 years. That helps to inform these discussions as well.

And after we think about what would be desirable, we then have to think about how to do it. Okay, what's technically feasible? What can be done? What can be measured? And what can we estimate resources for?

We have to have a specific enough set of activities that we're able to put an estimate of resource requirements around that. And so we look at what would be the resources required to do this.

If it's a very resource-intensive effort, industry may say, "Well, you know, that sounds like a nice enhancement, we don't know if our membership will

want to pay that extra amount of fees." And so there's a kind of discussion around that that you might anticipate having around any kind of negotiation to come to the place where there is mutual agreement about an enhancement and the resources required to do it.

We don't discuss regulatory policy changes. We consider the current statute to be a given; that's what we work with. And, as you can imagine, in that kind of discussion about what you would do and how it would be done and the resources required, the devil can be in the details, as we say, because if you change the details, it may change how technically feasible it is and the resources required to do it.

So that's the kind of discussion we've been having throughout each of these iterations. And I'm not going to go through each of them, but this is just to show you that we will be going into our sixth authorization of this program, so it's the most mature of the medical product user fee programs that we have.

And each one has had a slightly different emphasis and focus. The first was focused on trying

to clear out a backlog that existed at that time and trying to remove the drug lag that was experienced in the U.S. because we had an underresourced program.

Over time, we have addressed post-market safety issues; we have enhanced the capacity of that system. And we've improved our interactions with industry during drug development to make their drug development more efficient and predictable for them. And we get better applications as well as a result of that.

And, finally, in this most recent iteration, you will hear more about the further enhancements that we see to the pre-market review program and post-market enhancements, and is another area that we call decision tools, regulatory decision tools, which is a range of things that we're looking at generally piloting in a number of cases to see how we can use these methodological tools to further enhance the predictability and quality of the process.

This is just a timeline. And, again, you've probably seen this before. We cut off some of the front off this to say we started our discussions, our

user fee negotiations, in September of 2015, concluded those last winter, ratified those from the FDA perspective, and industry ratified it.

We put it through an administrative clearance process. And as soon as it was cleared in mid-July, we published our Federal Register Notice to basically begin to provide this information for the public to see the full details of the commitments that we were proposing to make, and so that you could begin submitting information to the docket and commenting in today's meeting.

And as Pujita said, we will close that docket next week and conclude the discussion, look at the information we've received, hopefully come up with a package that we can then send forward.

And, honestly, with all the changes that will happen over the next several months, there will be an administration change, for the first time during PDUFA we will have an administration change occur during the middle of this process, and there will also be congressional changes.

So our goal is to try to get this package up

to the authorizing committees before the end of the calendar year so we can really try to give it a smoother path, given all those other transitions that are likely to occur.

I'm certainly not going to read this, but these are the provisions that the statute lays out for us to follow for reauthorization. And I draw your attention a little bit, and you can read it later at your leisure, Section (4), Public Review of Recommendations. And this is the section that we're particularly focused on in addressing in today's meeting.

After the negotiations are completed, this package that we've put together, this presentation of materials, we publish it in the Federal Register, which is what we did on July 15th, provide at least a 30-day period for comment on that package, have a public meeting in which we'll hear the public views on these recommendations, and that's what we're here for today, and that's what we hope to hear and receive in the docket, and perhaps we'll hear from our folks on the webcast as well.

And then based on the recommendations and the comments that we receive, we'll revise, as needed, this package that we would like to then send on to the authorizing committees.

And so today's meeting is organized just as Dr. Woodcock was saying, three panels, the first focused on pre-market review and post-market safety, we'll go over. There are a number of initiatives in this package. We're very happy and excited about what's in there. We think it's going to make the program even stronger.

The second panel will focus on regulatory decision tools, and those enhancements.

And the third on a number of very critical administrative enhancements to the program.

And with that, I will turn it back over to Pujita. And, again, welcome today.

(Applause.)

MS. VAIDYA: Thank you, Theresa.

Panel 1 -- Pre-Market Review and Post-Market Safety

MS. VAIDYA: Now we will move into our panel presentations and discussions. Our first panel, as

Theresa just mentioned, will focus on "Pre-Market Review and Post-Market Safety."

So before we get started, could I please have our panelists come to the front, please? Great. Now that everyone is settled in, I would like to ask our panelists to please introduce themselves. I'll start from our FDA panelists here.

MS. TOIGO: Hi. I'm Terry Toigo, the Associate Director for Drug Safety Operations in CDER, and I led the post-market panel.

DR. JONECKIS: Hi. I'm Chris Joneckis. I'm the Associate Director for Review Management in the Center for Biologics. And I was on the pre-market review group.

MR. FREY: Patrick Frey, Senior Advisor in the Office of New Drugs, CDER. I was on the pre-market group.

DR. JENKINS: Good morning. I'm John Jenkins. I'm the Director of the Office of New Drugs in CDER, and I was the head of the pre-market group for FDA.

MS. BENS: I'm Cynthia Bens, Vice President

of Public Policy with the Alliance for Aging Research.

MR. MELMEYER: Paul Melmeyer, Associate Director of Public Policy at the National Organization for Rare Disorders.

DR. HAVEFIELD: Sascha Havefield, Senior Vice President for Science and Regulatory Affairs at PhRMA.

MS. HOLCOMBE: Kay Holcombe, Senior Vice President for Science Policy at BIO.

DR. ALLEN: Good morning. Jeff Allen, Executive Director, Friends of Cancer Research.

MS. VAIDYA: Thank you. So now I'll turn the mike over to Patrick Frey to go over the pre-market review recommendations.

MR. FREY: Thanks, and good morning, everybody. All right. I'm going to go through a few slides about pre-market review, and then we'll be turning it over for the post-market safety piece.

So many of you are probably familiar with the NME Review Program that we created in PDUFA V. This is a very successful program. We had an interim assessment and a public meeting about this program

last May, and before the end of PDUFA V, we'll be looking to have the final assessment concluded on that program as well as a public meeting there.

As we implemented the program and in the early years of PDUFA V, we recognized that there were opportunities to reduce the burden and the complexity of the program.

In some cases, review teams thought that the communication touchpoints in the middle of a review between the team and the company were somewhat duplicative of what they were already doing with companies in review of their applications.

In other regards, some of the specific activities that occurred late in the review process were very crunched and led to a lot of excess work during the review process after the primary review completed. And we also heard from industry that it was crunch time for them as well.

So we took this opportunity in PDUFA VI to make some changes, a big one being that we have the option between FDA and the company to agree on a formal communication plan during our review of the

application.

This may or may not include the specific elements, like the mid-cycle communication and the late-cycle meeting of the NME Program, and it can include other opportunities for communication. For instance, if the review team would rather just hold monthly teleconferences with the company, they can do that instead of holding a mid-cycle communication or a late-cycle meeting.

The important point is that the applicant and the review team need to agree on what this formal communication plan looks like. The agreement would occur very early in review, probably at the pre-submission meeting, and then there would be opportunities then to amend it, depending on how the review process goes, but any amendments would need to be agreed to by the review team and the company.

We made some slight procedural modifications during PDUFA V so that the program could accommodate expedited reviews. Those reviews are generally priority applications where the pressing public health need for the product indicates that we would like to

review it in shorter than the traditional PDUFA clock. So we codified them in the PDUFA VI commitment letter.

We also made some changes regarding applications that are filed over protest. So we refuse to file the application based on the quality of the application, but the applicant decides to file over protest. In those cases, the application would be subject to the program performance goals, the 8- or 12-month review, but they don't benefit from the additional communication that we see in the program.

We would generally not review amendments to those applications and we would not be submitting to the company any information requests regarding applications that are filed over protest.

And then any resubmissions that follow that first review cycle would not have performance goals associated with them.

We would also plan now in PDUFA VI to talk about review activities regarding our scheduling recommendation at specific touchpoints in the review process, like the mid-cycle communication, the late-cycle meeting, or any other communication

opportunities that are agreed to by the applicant and the review team.

Additionally, we decided to allow some flexibility of scheduling the Advisory Committee meetings.

This is what I spoke about early, late in review, when we have the late-cycle meeting, the Advisory Committee meeting falls pretty quickly after that, and there is a lot of preparation and a lot of background package work, discussions with the company that are occurring at that time, so we allowed a little bit more breathing room for the review teams and for the applicants in the timing of Advisory Committee meetings.

We also allowed for the option to have the review team and the applicant hold a quick follow-up teleconference to discuss the Advisory Committee feedback, if that is seen as helpful between the two parties.

Moving on, I'll talk about goal extensions for missing manufacturing facility information. This is a concept that was introduced in the PDUFA V

letter, and that regards the expectation for a comprehensive and readily located list of manufacturing facilities.

When we identify a facility that needs to be inspected and the information is not complete or easily found in the application, that can really throw sand into our review process.

So we decided that in PDUFA VI, when we need to inspect a facility that was not included on this comprehensive and readily located list, we may extend the goal date to allow for that additional time to go inspect that facility. So for an original application or efficacy supplement, that goal extension is our usual 3 months, and for a manufacturing supplement, the extension is 2 months.

Meeting management. In PDUFA V, we saw a real surge in the number of PDUFA meetings that we conduct with companies, and it topped out. We're not finished FY16 yet, but in the most recent fiscal year, it topped out between the two centers of over 3,000 meeting requests that we receive, and in most cases, we conduct those meetings, whether it's by a formal

face-to-face meeting or a Written-Response-Only option. Our denial rate for PDUFA meetings is incredibly low, on the order of 2 to 3 percent.

We also have experienced a phenomenon of increasing in length and in complexity background packages, and the current timeframe for reviewing them, which is 30 days, we get them 30 days before the meeting date generally. They don't allow enough time for our review and the internal meetings, sometimes multiple meetings are required to work through the questions that companies submit to us in their background package, so that we're able to give proper advice and well-thought-out advice, we needed more time to review these extensive background packages.

So in PDUFA VI, we will be creating a different type of meeting. It will be a Type B (EOP), End of Phase, meeting for certain End of Phase 1 and End of Phase 2 or Pre-Phase 3 meetings in the PDUFA program.

We have modified the timeframes, which are outlined in the commitment letter. In the case of these Type B End of Phase meetings and Type C

meetings, we'll be getting the background packages earlier. For the Type B End of Phase meeting, we will be responding to the meeting requests from the company a little bit earlier than we have previously.

And there are other aspects of the meeting process specifically that pertain to our consideration of the questions that companies submit to us and our responses that we send to them. There are timeframes for that so that the sponsors can consider our responses to their questions and then let us know whether they still need the meeting with us or whether the meeting can be narrowed more in focus and what questions actually need to be discussed in the meeting.

Sponsors may also request a Written-Response-Only for any meeting type now in PDUFA VI, and it is our decision at FDA to decide whether or not a Written-Response-Only is the right mechanism for responding to those questions. As in PDUFA V, FDA may issue a Written-Response-Only option for the pre-IND and the Type C meetings.

So nothing changes from FDA's standpoint,

but for companies, they can request a WRO for any meeting type. And that was based on some of our experience in PDUFA V where project managers were seeing companies request a WRO for a meeting that was not part of the WRO-eligible meetings in PDUFA V, and this will allow for that in PDUFA VI.

FDA-sponsor communication during drug development. Another really important aspect of PDUFA V is going to continue in PDUFA VI with respect to the staff that we have in the Office of New Drugs and that CBER has as well to both answer general questions about drug development, like where to find guidance, "Who is going to review my IND?" to serving as a facilitator if a company experiences challenges in communication with an FDA review team.

So the highlights of what we'll be doing in PDUFA VI include a third-party evaluation of current communication practices between FDA and companies during drug development. A workshop will discuss the evaluation results. And if the evaluation dictates or indicates the need for, we will update our draft or final guidance, depending on what it is at the time,

on our "Best Practices for Communication Between IND Sponsors and FDA." I think this guidance was out in draft in December of 2015.

Early consultations on new surrogate endpoints. So when a company intends to use a biomarker as a new surrogate endpoint for the primary basis of product approval, early discussion between the review team and the company is important.

So both FDA and industry recognized this during the PDUFA VI discussions, and our proposed approach is that these requests for early consultation isolated to use of a biomarker as a new surrogate endpoint for the primary basis of approval. These meeting requests will be considered a Type C meeting, and this meeting is to discuss the feasibility of the surrogate as a primary endpoint, what knowledge gaps exist, and what the path forward is to fill in those gaps.

This meeting, being Type C, is the only type of meeting in PDUFA where the meeting background package is due at the time of the meeting request. Sorry, we do, do that for Type A meetings now that I

think about it. But for these Type C meetings, the meeting background package is due when the meeting is requested because we recognize that these will be quite extensive background packages and require more than 30 days to get through them.

Combination product review. You heard Dr. Woodcock talk a little bit about this earlier. This is probably one of the more extensive new sections in the commitment letter. We recognize that this was an area that could be improved under PDUFA, our preferred vehicle for making such process-related changes.

And in PDUFA VI, we'll be developing the staff capacity across centers, not just CDER and CBER this time around, to more efficiently review these submissions.

We'll be streamlining combination product review, improving our ability to assess this workload as well.

In what follows from the streamlining of the review would be establishing MAPPs, Manuals of Policy and Procedures, to describe the review process and

procedures for combination products. We would also establish submission procedures and performance goals for FDA's review of human factors studies protocols.

A third-party evaluation will be conducted of combination product review, engaging both FDA and companies in combination products, and we'll be using these findings to update our MAPPs and corresponding SOPs, I believe, in CBER, if necessary.

And we'll be publishing or updating guidance on bridging studies and patient-oriented labeling.

Breakthrough was another critical new program in PDUFA V, and our observations, as this program got rolling, was that the workload was higher than anticipated in terms of the number of requests we receive, and then those also receiving breakthrough status, which, as we look at the breakthrough program, it's about a third of the requests that we get are granted breakthrough status.

So breakthrough represents a pretty big effort at FDA, and it's not just clinical disciplines, it's disciplines across new drug reviews. So in PDUFA VI, the resources will provide additional

staffing to the Agency to continue this work and interact closely with companies during development of their breakthrough products.

Rare disease drug development, another important part of PDUFA V, and we'll be continuing these activities in PDUFA VI. One thing that we'll be moving towards in PDUFA VI is to take the staff that we have currently in the Office of New Drugs and the Rare Diseases Program and be more fully integrating these staff into the review teams during the drug development programs and during application review. These staff will continue to be part of the Rare Disease Program but will simply be integrated more into review teams.

And we will continue our current and ongoing activities of the Rare Disease Program, which largely includes staff training, training that we hold here at White Oak, and invite people from the outside to also experience it, promoting best practices for review of these products, and conducting outreach that we've been doing over the last several years.

And now I think I will turn it over to Terry

to talk about a couple of slides regarding post-market safety.

MS. TOIGO: Thanks, Patrick.

There are two proposals in the post-market safety area that are focused on enhancing and modernizing the FDA drug safety system: one is the evaluation and communication of safety findings, and one is focused on Sentinel. I'll talk about the evaluation commitment first and then a little bit about Sentinel, although Dr. Woodcock already did quite a bit on Sentinel.

So FDA does understand that it's crucial to ensure clear, consistent, and transparent policies and procedures for communicating safety issues with industry, and more importantly, with the public. We do have process improvement efforts that are already underway to address management and oversight of post-marketing safety issues.

We are committed to using the PDUFA resources to improve our policies and procedures and systems for tracking and communicating safety issues, and then ensuring that these policies are of the

highest quality.

And as you can see from the slide, the commitment involves notifying sponsors when a serious safety signal is identified and about 921 postings, notifying industry 72 hours before a 921 posting.

And just to remind everyone, 921 notices are quarterly postings required by FDAAA when FAERS is the reason for the safety signal.

So, lastly, this commitment involves conducting an assessment of the data systems and processes that support the review, oversight, and communication of post-marketing safety issues.

Our second safety proposal is -- it's a mouthful -- Advancing Postmarketing Drug Safety Evaluation Through Expansion of the Sentinel System and Integration into FDA Pharmacovigilance Activities.

The Sentinel System has successfully completed its pilot phase, and it's now ready for full implementation into our FDA post-marketing review processes. The proposals build upon the commitments in PDUFA V. The challenge for FDA over the next PDUFA cycle is to ensure that the Sentinel System is

operationalized effectively and methodically in a way that maximizes the use of the system's expanding capabilities, so that we can actually realize the full value of the Sentinel System in our post-marketing safety review process.

We intend to use PDUFA funds to conduct a series of activities to systematically implement and integrate Sentinel into our FDA pharmacovigilance activities and practices.

First, the activities augment the quality and quantity of data available through continued expansion of data sources and the core capabilities of Sentinel, such as improving methods for determining when and how data can be used.

Second, we'll enhance communication with sponsors and the public regarding the general methodologies for Sentinel queries, and then the lessons learned from using Sentinel. And we do a lot of that already. The PDUFA commitment supports continued and enhancing those communication efforts.

And then, finally, as we have done with PDUFA V, we will analyze and report on the impact of

the Sentinel expansion and integration on FDA's use of Sentinel for regulatory purposes. And that's our post-market commitments.

And so now I'll turn it back to Pujita.

MS. VAIDYA: Thank you, Patrick and Terry.

Now I would like to ask our panelist stakeholders to provide their views on the recommendations that were just provided. And we'll start off with Cynthia Bens.

MS. BENS: Good morning, everyone. I just want to thank FDA for inviting me to be on the panel today. As I mentioned earlier, I am Cynthia Bens, Vice President of Public Policy at the Alliance for Aging Research, but I also serve as Executive Director of two Alliance-led coalitions called Accelerate Cures and Treatments for Alzheimer's Disease and the Aging in Motion Coalition.

I only have 3 minutes, so I'm going to be uncharacteristically brief and not go into too much background on the coalitions except to say that we've been working with FDA, patients, the advocacy community, and industry on clinical trial challenges

with both Alzheimer's disease and more recently with sarcopenia in older adults. These are two incredibly challenging disease areas to develop clinical programs for.

We feel that our coalitions have provided a meaningful conduit to facilitating really meaningful communications between FDA and the stakeholder community, but one thing that we really realize is how important early and ongoing communications are between FDA and sponsors throughout the drug development process.

And we think that PDUFA VI makes really meaningful changes to both internal and external FDA communications related to communications across the drug development process.

And I'm just going to make a few comments related to advancing regulatory science and also expediting the drug development process.

First and foremost, the Alliance supports the utilization of user fees under Section I, Number 1, to maintain dedicated staff within CDER and CBER focused on improved communication between FDA and

drug sponsors.

We're encouraged to learn that the staff is going to continue providing ongoing support on training for the review divisions on appropriate communications with industry sponsors, and at the same time, working to facilitate responses to general inquiries, as Patrick mentioned earlier, ensure timely resolution to specific issues related to specific INDs.

We also support the user fees that are going to be used for the independent assessment of current practices, and are happy to see that this is going to be part of a public workshop within IDA (ph) issuing revised guidance, if it turns out that that's necessary.

The second provision we support in PDUFA VI is Section I, Number 3, early consultation on the use of new surrogate endpoints. The meetings described in this section are going to allow for companies to engage with FDA senior leadership on the feasibility of using a surrogate endpoint that hasn't been used previously on the basis for an approval and also help

identify critical knowledge gaps that need to be filled and help to create a plan for that.

We don't yet have current qualified biomarkers for either of the disease areas we work in, but we know how critical the use of surrogate endpoints are going to be as we're moving earlier in intervention, particularly in Alzheimer's disease. So establishing this dedicated process for meetings on surrogates that can occur as early as end of Phase 1 or Phase 2, it's really a priority for us.

The third provision that's important to the Alliance is Section I, Number 5, advancing the development of combination products. It's expected that the number of products in development that are going to be combinations is going to increase to almost 40 percent. Because of the significant increase, it's important to us that FDA is able to ensure that drug device and biologic device combinations don't face unexpected delays in the review process.

We're pleased the PDUFA VI is going to provide funding for capacity building, staff training,

and also set performance goals for CDER- and CBER-led combination product activities.

The final provision we support in Section 1 is the addition of user fees for the Breakthrough Therapy Program, and anybody who attended the kickoff meeting last July knows that this is something that was very important to us, and I know it's going to be important to Jeff Allen, too.

During the kickoff meeting, I talked about the strain that the creation of the Breakthrough Therapy Program has had on the Agency because it didn't provide additional resources under PDUFA V. PDUFA VI will allow for the addition of 36 FTEs to assist with expedited approval pathway.

And Breakthrough has really been transformational for a number of disease areas that are serious and life-threatening. We'll be glad to see it continue and we really hope that in the near future it's going to be utilized for both Alzheimer's disease and sarcopenia treatments.

So I'm going to stop there, and I look forward to answering any questions from the rest of

the panelists.

Thank you.

MS. VAIDYA: Thank you, Cynthia.

I'll turn it over to Paul next.

MR. MELMEYER: Thank you very much. And thank you to the FDA for the invitation to participate today.

I am Paul Melmeyer. I am the Associate Director of Public Policy at the National Organization for Rare Disorders. And we represent all 30 million Americans with rare diseases. In doing so, we provide various services to the rare disease patient population, including policy and advocacy support, educational services. We're a member-based organization. We have over 250 rare disease patient organizations under our wing.

And then we also develop rare disease natural history registries with our member organizations actually in partnership with the FDA.

So we've been very pleased to participate in the PDUFA reauthorization process for the last 13 months. And we participated in the July 15, 2015,

kickoff meeting. And in that meeting, we presented several of our PDUFA reauthorization priorities, including funding the FDA appropriately through dedicated user fees, strengthening and incorporating the patient voice, and participation throughout the drug development and review process, promoting consistency across review divisions in using flexible drug review opportunities and resources for rare disease therapies, and then several other policy proposals that we'll be talking more about over the next year, particularly with our congressional colleagues, so apologies already to you clean PDUFA'ers out there.

And I think we see a lot of alignment within the commitment goals letter for what we were hoping to see within the PDUFA reauthorization process.

Specifically within the jurisdiction of this panel, I suppose, the funding of the dedicated user fees for the Breakthrough Therapies Program is very important to us within the rare disease community. Many orphan products take advantage of the Breakthrough Therapies pathway, particularly within

rare cancers. We're hoping the Breakthrough Therapies pathway will be expanded a bit further into rare inherited disorders as well.

And we hope that the funding of the Breakthrough Therapies pathway through dedicated user fees will allow that to be done. And I won't say any more on that because having Jeff on the panel and talking about Breakthrough Therapies seems superfluous.

And the same goes for the Office of Combination Products. There are many rare diseases that are treated through combination products oftentimes because rare diseases require some kind of innovative route of administration. So dedicated funds going to the Office of Combination Products will facilitate the review of those orphan combination products.

I think the primary reason I was invited, however, was to speak on the Rare Disease Program, Rare Disease Office expansion within CDER. And we're very encouraged to see this piece. The Rare Disease Program within CDER was instituted back in 2010 to

really address the inherent problems and difficulties within orphan drug development, including the fact that there is very little oftentimes no natural history data or scientific understanding within particular rare diseases, very few established and reliable diagnostics, virtually no biomarkers whatsoever.

They're very small and dispersed patient populations that oftentimes have very heterogeneous clinical manifestations.

Two-thirds of rare diseases affect children, and 80 percent are of genetic origin. And many rare diseases are actually caused by various different interacting genetic mutations.

So all of these inherent difficulties within rare disease drug development require a certain amount flexibility within FDA review, and we've been very encouraged to see that flexibility.

We co-authorized a white paper in 2014 with Frank Sasinowski, of Hyman, Phelps, that showed about 67 percent, two-thirds, of orphan therapies enjoyed some sort of flexibility within FDA review. And

actually I've seen more recent data that showed upwards of 75 percent of orphan therapies enjoyed some sort of flexibility within FDA review.

But we can still do better. We're still hearing from our patient organizations that FDA may be requiring an extra confirmatory trial or what they view as a particularly arduous control, maybe even a placebo control, as well as perhaps too narrow inclusion criteria, and maybe not enough of an emphasis on quality of life improvements for particular orphan therapies.

So with the expansion of the Rare Disease Program into the review divisions, we're very encouraged that those viewpoints and those points of view within the rare disease community will be better reflected within each review division.

And if we can make one request within this particular piece, it would be for these individuals within each review division to be publicly accessible and to proactively reach out to the rare disease patient community and actually get to know the patients for whom they'll be reviewing the drugs, so

that they'll actually be able to go to the conferences that a patient organization will be putting on and to actually have someone in mind, have a patient that they've met in mind, when they are looking at a potential application in front of them within their particular review division.

So I'll stop there and thank you again for the opportunity.

MS. VAIDYA: Thank you, Paul.

Next I would like to turn it over to Sascha.

DR. HAVEFIELD: Good morning, everybody. I'll keep it very short as well. After Cynthia, Paul, Terry, and Patrick have already gone through all of the details of the agreement, let me just start by saying that I'm very grateful for the opportunity to participate in today's PDUFA VI Public Meeting and to discuss the benefits of the agreement for public health for the FDA's Human Drug Review Program for Biopharmaceutical Innovation, and, most importantly, for the patients we serve.

FDA's Human Drug Review Program is recognized as the global gold standard, and the PDUFA

program is essential to the Agency's continued ability to enhance and sustain its review of innovative new drugs and biologics. For patients, this has meant faster access to over 1,500 new medicines while strengthening FDA's appropriately high safety and efficacy standards.

PDUFA VI not only continues the successful NME Review Program, as you've already heard, but includes enhancements in areas such as communication between the Agency and sponsors during drug development and regulatory review, targeted consultations on the use of innovative drug development tools, I think as Cynthia already highlighted, streamlining the review of combination products, providing resources for the successful Breakthrough Therapy Program, and a continue focus on investment and post-market safety activities.

So let me just touch on a couple of or a few additional provisions here in more detail. The NME Review Program 2.0, as I think it was referred on an earlier slide, the NME Program has been very successful. As total review times have continued to

decline while first cycle approvals have increased compared to previous PDUFAs and PDUFA V, where the NME Review Program was introduced.

PDUFA VI not only continues the NME Review Program, but strengthens it in important areas, such as expedited reviews, breakthrough therapies, and drug scheduling of NMEs.

Other provisions would be combination product review. Combination products represent important treatment options for patients as we move into an era of personalized medicine. And PDUFA VI will help streamline the FDA's combination product review process and enhance related Agency capabilities; the same for the Rare Disease Drug Development Program.

And, Paul, as you just highlighted, the focus on rare diseases in the past, or in past PDUFAs, has yielded significant advances in development, review, and approval of new treatments for rare diseases. As an example, in 2015, 90 percent of all breakthrough therapies approved by the Agency were for orphan indications, and that is a clear measure of

success and shows how orphan research and orphan drug development has been integrated into the heart of drug development discovery and the regulatory review process at the FDA.

PDUFA VI continues these efforts and will advance the development and approval of innovative medicines for the treatment of rare diseases, including pediatric rare diseases, very importantly.

From the information that Terry reviewed for us, communication of post-market safety findings and the expansion of Sentinel, the PDUFA program provides the necessary resources to review and approve new treatments for patients, but just as importantly, dedicates substantial resources to help ensure the continued safety of medicines when they are on the market.

PDUFA VI includes a $50 million investment to expand the Sentinel System's capabilities and enhance the communication process with stakeholders on the use of Sentinel data, as you have heard.

I wanted to touch on one more item, Paul, that you also highlighted about Breakthrough Therapy

resources and fees, and I'm pretty sure we will actually discuss this later on in the third panel when we go over changes to the user fee structure.

The user fee structure for Breakthrough Therapies, there isn't a single Breakthrough Therapy fee, but Breakthrough Therapy is a part of the NME review program or part of the new Human Drug Review Program, and, as such, are funded by the general fees that are collected from biopharmaceutical companies going forward.

It's just one of those issues that I think we've been asked multiple times because the user fee collection schedule is very complicated, that we always have to remember that all user fees are collected and made available to support the full program at FDA, the Human Drug Review Program, and then are allocated appropriately by the Agency.

With that, thank you very much, and I'll hand over to the next presenter.

MS. VAIDYA: Thank you, Sascha.

I'll turn it over to Kay now.

MS. HOLCOMBE: Thanks very much. BIO

appreciates the opportunity to be here with you today and greatly appreciates the opportunity to be part of this historic PDUFA VI negotiation.

We had some priorities in mind at BIO when we entered this PDUFA cycle over a year ago. First, the voice of the patient must be heard, listened to, and incorporated throughout drug development and product review and into FDA's regulatory decisions.

Second, FDA must be able to attract, hire, and retain excellent scientific and medical personnel. If they are unable to do this, regardless of the lofty goals of PDUFA, we will not be able to achieve those goals.

Three, the watchwords of "communication," "consistency," "timeliness," and "flexibility" must be fundamental in the lexicon of FDA's stakeholder interactions.

Four, the long-term stability of PDUFA must be guaranteed by financial accountability, transparency, and movements to assure that this program can remain viable into the long-term future.

And, finally, enhancements must be pursued

in the review process so that we can incorporate 21st century tools and emerging technologies without at all lowering FDA's excellent standards for safety and effectiveness of drugs.

PDUFA is a two-way street. It is this commitment letter plus the commitments that are made by industry to do things that will help this commitment letter work.

So first of all and a long time ago in negotiating PDUFA, we heard from FDA loud and clear that part of the responsibility for getting a timely and effective review was our responsibility in industry. We need to make a commitment, and we have made that commitment, to submit complete and thorough applications of high quality to the FDA.

One of the things that Patrick Frey mentioned reflects another commitment of the industry, and that is a commitment of the industry to include in its application all of the facilities where it will be manufacturing its drugs and biological products. Isn't it shocking to think that we were submitting applications where we were kind of not mentioning

where we were going to make these things?

We need to provide FDA with timely and thorough background packages for meetings because if we don't do that, FDA will not be able to be prepared to give us the answers to the questions that we have when we ask them for meetings.

We need to be committed in our industry to provide FDA for increased resources that are required for them not only to carry out new initiatives that people think of during each PDUFA cycle, but also to carry out initiatives that we all agree are in the public interest and in the interest of patients, but for which, for whatever reason, there are insufficient resources, and breakthrough therapies is a classic example of this.

This is an excruciatingly important program, a highly successful program, for which FDA was never resourced to do it the way they needed to do it. I think everybody was surprised at how popular the program was, and it was, for us, one of the great ideas of all time, and we want to thank Jeff for this great idea. It was his idea, really, seriously.

But we made a commitment under this PDUFA to increase resources so that FDA can carry out, continue to do the Breakthrough Therapy Program, and carry it out as we move into the future, and there is more interest in doing that.

Sentinel is another example of that. Congress required FDA to establish the Sentinel Safety System, and did indicate that user fees need to be supporting the Sentinel System.

With the expansion of Sentinel from Mini-Sentinel, which was going on over the last 4 years, to full use of Sentinel, we are going to need to provide additional resources. And our industry is committed that Sentinel should work the way it was intended to work. It is one of the great examples of the importance of real-world evidence.

This is real-world evidence here in Sentinel on hundreds of millions of lives, and it is evidence that FDA can use and we in the industry can use to make sure that products continue to be safe as they are used by more and more people in the marketplace. So we are very happy to have made the commitment to

expand our support of this expanded Sentinel System.

And I just want to mention one more thing because everyone has mentioned a lot of the really significant commitments in this landmark PDUFA VI agreement, but I would be remiss in my responsibilities at BIO if I did not mention one of our most important initiatives, and that is the initiative that began in PDUFA V with the establishment of the FDA Communications Office, and will continue in PDUFA VI to develop best practices and translate those best practices for communication across all of the review divisions at FDA.

This is an extremely important issue, especially for many of our small companies who are entering their first experience with FDA. They don't know who to talk to or how to do it right. So the help that they have received from this Communications Office and the dedication of the Office of New Drugs and others at FDA to making this communication with our companies more effective is something for which we are extremely grateful.

So I'm not going to mention any more

programs, but I want to say that we at BIO strongly support this PDUFA agreement, and we thank FDA for some of the great ideas that they contributed and for taking our even better ideas.

(Laughter.)

MS. VAIDYA: Thank you, Kay.

And, finally, we have Jeff Allen.

DR. ALLEN: Good morning. I would also like to thank the FDA for the invitation to participate in this meeting today, and I really would like to certainly lend our support to the contents of this agreement letter, as others have already this morning, and also take just a minute to congratulate the negotiators, both from the FDA and the industry side, for the commitment to a timely reauthorization of this process, the thoughtfulness, and rigor that went into the process.

I'm sure we only know the tip of the iceberg from what was provided to us at the third-party stakeholder meetings, which we, of course, appreciate, on both sides, the updates as well as not necessarily having to be into all of the trenches that you've all

been through, but certainly congratulate all of you on the work done here, which we're very pleased to support.

I've rewritten some of my notes, because I feel obliged to say something about Breakthrough Therapies, but I think Dr. Woodcock noted in her opening remarks that the 5-year cycle of the PDUFA reauthorization provides the opportunity to evaluate and, where appropriate, improve the program, and I think that it is an important process, and it also allows time to reflect on opportunities where development and regulation can evolve with the rapidly evolving pace of science. And there are many things, both within this agreement letter that I think are build on that principle as well as it has in the past.

So with regards to some of the contents here that we think are quite important, I certainly can't take any responsibility for the Breakthrough Therapy Program largely. I think this belongs to the leadership at FDA, who, even before it was coined a Breakthrough Therapy designation, showed multiple examples where four areas of unmet medical need for

new therapies that have the potential to show substantial clinical benefit, that they were able to work with sponsors and expedite the development of these new drugs.

I think together we just gave it a name and hopefully gave it some processes, but they deserve the credit in frankly doing this already in many instances. So we're very appreciative of that as well as the commitment to make sure that it continues.

I think that it is a surprise -- I agree with you, Kay -- that in a little over 4 years the fact that we have seen over 400 requests for a designation, 145 designations that have been granted by the Agency that has already led to 46 products that have been approved through this program is really remarkable.

So we're, of course, extremely supportive of the ability to apply resources and make sure that this program can continue. It is very intense on both behalf of the Agency as well as the industry in order to try and expedite the development of these products.

And this leads to some of the, I think,

important flexibility and communication advancements that are in I, Number 1, at least anecdotally, and maybe that's still where we are in terms of evaluating the Breakthrough Therapy Program. The intensity of communication and the flexibility around that has really made this program, in particular, a success.

We hear anecdotes of how much more the meeting structure in many ways isn't applied, but it's almost a Breakthrough Therapy hotline where reviewers are picking up the phone to ask questions, and there is this back-and-forth that is extremely labor-intensive, and we haven't figured out a way yet, although I hope we're working on it, to add more hours in the day to allow for this additional work, especially in areas where it's so critical.

And we've seen a lot of success around this program. We tried to do sort of a quick back-of-the-napkin calculation that we published about a year ago that looked at the development time of breakthrough therapies, not just the review time, which I think people tend to focus on, but that's such a short component of actual product development, but with the

goal of Breakthrough Therapies being to expedite the entire development program.

What we found from the time of filing an IND to the actual approval in oncology for over the 4-year period where data has been available, that products with a Breakthrough Therapy designation were able to go through the development process in over 2 years' shorter time.

So while it's a crude assessment for a number of reasons based on things like the natural history of the diseases and things like that, these are all oncology products, and while it may not be exact, we're certainly seeing something here in terms of the ability to expedite development in these instances.

And I think a vast majority of the reason of this is we also found that many of these products, about 70 percent of them, utilized accelerated approval, which I think speaks to the importance of the consultation program that's been put into place here around new surrogate endpoints.

I hope this is a stepping stone for future

programs that could be looked at. I understand why this does need to be a stepping stone, because the Agency is not resourced to be able to be answering random questions on biomarkers, and I'm not suggesting that that's the case, but I think this is a good start by looking at the feasibility for a surrogate as a primary endpoint.

But there could be more opportunities here in the future looking at expanding a program beyond just a biomarker used as a surrogate, but for this to be a broader scientific tool to understand the development of new surrogates, not just in the context of that application at hand, but to inform the field moving forward.

One thing that I would like to perhaps add to the language here, or at least suggest as this is implemented, where it reads at the time the request is made that include preliminary human data indicating impact of the drug on the biomarker, we certainly would support also data on the impact of the biomarker on overall health outcomes as an important part of this since we have seen in the past where it's not

just the biomarker that we're interested here.

But I think this is a great stepping stone forward. It will certainly support the advancement of new breakthrough therapies and drug development more generally. So, again, we certainly appreciate the efforts that have gone into this and look forward for implementing these programs in the years ahead.

MS. VAIDYA: Thank you, Jeff.

So it is 10:08 right now. First of all, I would like to thank all of our panelists. And we will be breaking now for about 15 minutes and reconvening at 10:25. Thank you.

(Applause.)

(Break.)

Panel 2 -- Regulatory Decision Tools

MS. VAIDYA: We are now ready to begin our next panel session, focused on regulation decision tools recommendations. I would like to ask our panelists to please introduce themselves. We can start off with Diane.

MS. MALONEY: Good morning. I'm Diane Maloney. I'm the Associate Director for Policy at the

Center for Biologics Evaluation and Research. And I was on the regulatory decision tools group. Thanks.

MS. TOIGO: Hi. I'm still Terry Toigo, Associate Director for Drug Safety Operations. And I was not on the group but did real-world evidence, and that's my section.

DR. ZINEH: Issam Zineh, Director of the Office of Clinical Pharmacology. I was on the pre-market group as well as the regulatory decision tools group.

DR. LAVANGE: Good morning. I'm Lisa LaVange, Director of Biostatistics in CDER and also on the regulatory decisions tools group.

DR. MULLIN: Hi. Theresa Mullin again. And I direct the Office of Strategic Programs in the Center for Drugs. And I headed up this regulatory decision tools little subteam as well as the overall negotiation team.

And I'll just add in case she doesn't, but Pujita Vaidya served as our very effective project manager, and that's how we managed to get it all done and get it written up, so I just want to throw that in

there.

MS. VAIDYA: Thank you, Theresa.

MS. JAPHA: Good morning. I'm Maureen Japha, Director of Regulatory Policy at FasterCures and legal counsel for the Milken Institute.

MR. BOUTIN: Good morning. I'm Marc Boutin, the CEO of the National Health Council, an umbrella organization of patient advocacy organizations, which provide a united voice for people with chronic disease and disabilities.

MS. KENNEDY: Good morning. I'm Annie Kennedy, Senior Vice President for Legislation and Public Policy for Parent Project Muscular Dystrophy.

MR. KREMER: Good morning. I'm Ian Kremer, Executive Director of the LEAD Coalition. We're a coalition of 90 dementia-serving organizations.

DR. HAVEFIELD: And I believe I get to do this one more time on Panel 3. I'm Sascha Havefield for PhRMA.

MS. HOLCOMBE: Kay Holcombe.

MS. VAIDYA: Thank you. Now I'll turn the mike over to Theresa to kick off this session.

DR. MULLIN: Thank you, Pujita.

So we're going to do this one a little differently because the regulatory decision tools actually are a set of tools that have different disciplinary expertise involved in their implementation and in crafting these proposals. And so we've asked the lead architects to help here.

So Dr. LaVange is going to talk about the ones that have to do with statistical methodology. And Dr. Zineh is going to talk about the ones that have to do with the model informed drug development and biomarker qualification. And Terry Toigo, as she said, is going to cover our real-world evidence component.

So we're just going to mix it up a little bit like that.

So I'll begin with the enhancement that has to do with incorporating the patient's voice in drug development. And I think most of you, and certainly FDA, going into the negotiations in last July, I mean July 2015, we also identified the patient-focused drug development as one of our key areas, one of the areas

where we wanted to enhance and further expand on that. And what we noted, a couple of things we noted, and I'll just mention things that a few of you said in the room.

So July of 2012, I guess it was, I remember Diane Dorman -- and she's here today -- came in and met with us and congratulated me on getting the reauthorization because that just happened that July, and all the things we had in there, and great job on patient-focused stuff and everything like that, she said, "But I notice that you only have 20 meetings that you're planning to do, and we at NORD alone --," she was with NORD at the time -- "We alone have 7,000 diseases that we represent. How's that going to work?" And she said, "I bet you're not going to make them all rare either."

And that was the beginning, when we realized that, yes, we have to come up with some way where FDA is not the necessary party to everything, that we have to pilot this and figure out how to do it so that the rest of the community can take on and do as much of it as they can and that they're able to do because we

don't want to be the bottleneck. And so that's been our thought throughout.

And another observation that we made in the course of the meetings we've done so far, we're almost up to 20, we might even be at 20 at this point. I'm looking at Pujita because she's very involved in those meetings as well, but we're going to go beyond the 20 we promised to do, we're up to doing at least 24. And we put together these externally led meetings because, again, others can do this meeting and have these meetings with patients, and we're not able to meet the demand and all the diseases that need to have this kind of an exchange and get to hear from the patient community.

But the other thing -- and Paul said something I thought was very important in the earlier panel about the value of reviewers hearing what patients have to say. And certainly if you've been in some of those meetings, if you've been able to attend some of the meetings we've had to date, they're extremely powerful. These patient-focused drug development meetings are focused on a particular

disease area. We work hard with the community to try to have as many people come in person. We have a pretty effective webcast participation. And the meetings are extremely powerful. You hear directly. They're intended to just hear from the patients.

And what we learned from that -- and it energized us -- is to say the stories we were hearing are extremely important and valuable, and they give us insight, but they're not a replacement for data, and we really did need to figure out, how do we move this into more of a scientific approach, and in some groups, and I know, for example, FasterCures talks about the science of patient input.

So we thought we really need to bring in more methodology and again provide tools to people so that we can go beyond the very powerful stories to getting this in a form that's rigorous enough, fit-for-purpose, so that it can be a basis for regulatory decision-making, we can treat it as data.

So that's to give you an idea of what we learned and some of what was behind our thinking for the enhancements for PDUFA VI, also just recognizing

this very basic fact that patients are experts in what it's like to live with their disease and the burdens of treatment that they may be experiencing. Even as they take the treatments and benefit from it, there are often burdens associated with it. It could be the adverse effects, it could also be the regimen, or both. Typically it's both and beyond, and their families.

And so with that in mind, we saw this opportunity to develop a more systematic approach to bridge from these patient-focused meetings, which are a very important preliminary early piece of trying to get meaningful patient input into the regulatory decision-making process and into informing us about a particular product, and how to do that.

And so we've put together a proposal that begins with a series of guidances that are needed, and these guidances are complementary, they're actually a sequence, a logical sequence, that build the information, and we'll be producing them over a series of years because each one is a pretty heavy lift.

So we are basically going to conduct a

public workshop a number of months before the guidance comes out to help inform the guidance development so we can hear other parties, experts, patient groups, researchers, industry researchers as well, and helping us with the best of their information to inform what we put together in these guidances.

So there are four of them. The first would be how to collect comprehensive patient community input, and do that in a way that represents the community, and to collect that information about the burden of disease and current therapies.

The next guidance, on development of a holistic set of disease or treatment impacts that matter the most to the patient.

And then, how do you develop measures of that identified impact? And you want measures that are going to basically move and be responsive to treatment so that they actually serve some value in a trial to help measure benefit.

And the last guidance we talk about doing with this structure of public meeting workshop and then months later draft guidance is one on clinical

outcome assessments and how to better really incorporate this information into endpoints and trials.

And then about 18 months after we publish the draft or we close the comment period on that, we will try to produce a final guidance.

So there's a lot of work there that's intended to provide the tools to the community and to industry to basically do this work.

We are going to be at the same time revising our MAPPS, our Manuals of Policy and Procedures, and our Standard Operating Procedures, to give the reviewers and people within the centers the information they need to effectively incorporate this and pull this into their review processes. And so we have the sort of symmetry, if you will, of the outside guidance and these inside MAPPs.

We're going to build a repository and maintain a repository of publicly available information that we would have about meetings that are going on with patient groups, tools that are available that could be shared we can talk about.

So that at least I know there are others working on providing kind of a one-stop shop, and we're going to do our share there as well to try to minimize the duplication of effort because we know that patients and the patient advocacy groups, everybody wants to use their resources as smart and efficiently as possible -- smartly I guess I should say -- and efficiently as possible. And so providing places where people know to go look and see what others have done are useful. And so we're going to provide one of those.

And, finally -- and this is quite critical -- we're going to expand the capacity in our review divisions to be able to do this work. We have literally a handful of statisticians in the Center for Drugs who specialize in this kind of review today, and not much more, maybe two hands, in the Office of New Drugs, and that's it right now.

And we need to build the capacity with people with the expertise to do this work and who can work closely with the others in the review divisions as part of an integrated multidisciplinary team to

accomplish this work and really integrate it because involving the patients' perspective is actually going to involve a bit of a culture change.

And those of you who are in other meetings related to this, we know that not only at FDA, but throughout the health care system and even in big companies and elsewhere, that involving patients in this way is a change, and it's going to take a sustained effort for all of us to do it right, and that's our goal here.

So the next enhancement I'm going to talk about is benefit-risk in regulatory decision-making. This is also an enhancement that started out, we had an effort in PDUFA V, and we're building on that effort. So this is about building on our benefit-risk assessment, which focused in PDUFA V on the point of pre-market review, the NDA/BLA review.

In this case, we're going to update that guidance on benefit-risk implementation, and it's got a rather long name -- all of our documents have long names -- "Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making."

We are going to have a guidance that really looks at how we would use benefit-risk throughout the life cycle. So starting in the early stages of development, what kind of questions related to benefit-risk assessment can be addressed at that point when there is not a lot of data about this new molecule? all the way through to post-market safety.

When new information is coming in, you have a much wider base of experience. What questions do you ask about benefit-risk assessment at those later stages of the life cycle?

In this as well, we're going to be continuing to evaluate our implementation of the benefit-risk framework and look at where the best practices and the most successful uses have occurred so we can replicate and expand on that. And we're going to also modify our MAPPs and SOPs as needed here to incorporate those best practices and make sure that we're building on that.

With that, I'm going to turn it over to Lisa to talk about innovative trial designs.

DR. LAVANGE: Thank you, Theresa.

I'll talk about two proposals in the regulatory decisions tools group -- sorry, regulatory tools group -- and the first has to do with innovative trial designs. This was a proposal that came from both sides of the negotiating table. My counterpart in the Center for Biologics and I had talked. We had had some internal discussions about how to better convey to sponsors what is required on submission of innovative designs and then how to better review those once they come in-house.

And I think that both sides felt this was important due to a general awareness that the use of potentially efficient or effective innovative trial designs was low due in part to some lack of clarity of whether they would be accepted by the FDA, and if they were, what needed to be submitted in addition to just the datasets to show that these designs were working as they should.

So we came up with this proposal that we're very excited about, and the idea is to advance the use of these approaches when they make sense, when they're fit for purpose for the drug development program and

to clarify for sponsors what we expect.

Now, what happens with these innovative designs is that often their operating characteristics, such as the type I error rate or the power, are not able to be solved mathematically, there is not an analytical derivation of those quantities, and so computer simulations are required, and computer simulations have to be run over all the different types of things that can go wrong.

We are most interested in what can go wrong in terms of a false positive result. The sponsor is most interested in the power, but we're interested in that as well. And they're harder to review in that case because we can't just check a number and say, "Oh, here's the type I error." We have to agree with the sponsor on what that would be.

So we're focusing on the designs that do require these simulations, and that's what makes the submission and the review a little bit more difficult.

So what we've proposed, first of all, is to enhance our staff. We need to make sure we have the right staff with the right training and sufficient

quantities of staff, quality and quantity, to be able to analyze and review these complex designs. And they may or may not include Bayesian designs. There are plenty of complex adaptive designs that are not Bayesian, but we are also interested in the Bayesian designs, which almost always require simulation to figure out the operating characteristics.

And so what we envision is hiring more statistical analysts with strong computing and, in particular, simulation skills for this purpose as well as to continue to recruit mathematical statisticians as reviewers.

And we then want to conduct a pilot program. We thought this was a really good idea for a couple of reasons. First, if the submission qualifies for a pilot program, then you get a couple more meetings, it's actually a pair of meetings, to discuss what simulations need to be conducted by the sponsor and submitted to the FDA; and then also how, after we've had a chance to look at it, to meet again and discuss if there are shortfalls, what additional simulations are needed, what our simulations may have come up

with, and so forth.

So the additional meetings is the attraction, but we're also hoping that this might enable us to have more of these designs in the public domain that can be discussed at scientific meetings. Right now, there is a paucity of examples that we can use to explain what we will accept, what we won't accept, what we thought about them, because we don't talk about submissions.

So this would require a willingness on the sponsor's side to let us have some discussion of these designs in public. And there's a control for how many of these we can take. I think it's two per quarter, one CBER, one CDER, and we may not have that many submissions. But that's our hope for the pilot program.

We also plan to conduct a public workshop. We'll need to figure out the timing of this. It could be prior to the pilot program, it could be during or after the pilot program, and serve as a vehicle for discussing some of the things that have been submitted. But I think we might want to go ahead and

have the workshop so we can at least have an open dialog about the full range of these innovative designs and clear up any confusion as to what we're interested in.

And then we will develop a guidance that will better clarify what's acceptable, what's not acceptable. It will be very principle-based, it won't necessarily give you a litany of designs, but talk about the principles upon which we decide what's acceptable.

And then internally, we'll figure out what we need in terms of SOPs and our own internal procedures primarily because these designs will require probably more simulations on our part, and our reviewers need clarity. How many simulations? What are we trying to show with our simulations? Do we have to do things the sponsor didn't do? Do we just repeat the sponsor's simulations? And then in terms of what we're looking for on a submission. Does the sponsor just give us the results? Do they give us their program code? The random number seed? All of the little aspects that will make the submissions

hopefully easier for the sponsors to get in to us and easier for us to review. So hopefully that was clear.

And then the second is about analysis data standards. So there are lots that have been going on with PDUFA in terms of the standards surrounding electronic data submissions. But we review analysis files, and there are some things that we think we can ask for to enhance the analysis file review and similarly for sponsors, it should accelerate the review and certainly improve the communication when we're trying to reproduce analyses. And this is any submission, not just the innovative designs I talked about.

So our approach here is to enhance our staff capacity to more efficiently review analysis file datasets, and this includes having more staff available to work on the therapeutic area standards for these types of analysis datasets.

Analysis datasets can get pretty complicated in terms of the variable creation and coding, missing data elements, when you're building a scale and so forth. So we're hoping that if we can set up some

good standards for the analysis files and encourage their use and educate folks about them, that will improve the timeline in terms of the statistical review.

And then similarly, to the previous project, we want to convene a public workshop to talk about the development of these standards and how they can be used to facilitate the review.

And then we'll work on SOPs internally so that our reviewers are not reinventing the wheel and taking advantage of the analysis data that are submitted to us using these standards.

So I'll turn it over to Issam for the next two.

DR. ZINEH: Good morning. It's a pleasure to provide context and overview for two proposals that in many ways represent the culmination of work from a lot of stakeholders over at least 10 years, probably closer to 2 decades, depending on how you count time.

The first one is on model-informed drug development, and for those that have not had exposure to the concept, model-informed or model-based drug

development is the taking of our understanding or observations of disease biology, physiological processes, drug interventions, turning those into mathematical computational models, and leveraging that information in drug development and regulatory evaluation.

The success of model-informed development has been communicated extensively in the peer-reviewed literature by regulators and by industry scientists. It results in usually clinical trial design enhancements in the form of shorter trials with fewer patients, increased probability of regulatory success when we're talking about approvability or labeling or fewer post-marketing requirements or commitments, and optimized drug dosing and therapeutic individualization in the absence of dedicated trials.

But for a variety of reasons, model-informed drug development has been heterogeneously applied and accepted, and this enhancement proposal is intended to address some of those reasons.

So first, the enhancement intends to convene a series of workshops to identify best practices in

the model-informed drug development space. We have at least four that have been enumerated in the commitment letter.

The second is to conduct a pilot program that allows for direct engagement between drug development scientists and scientists on the FDA side that have particular expertise in these areas. And so this is not different than the pilot program that Dr. LaVange talked about in terms of providing direct access to scientists to get at some of the technical matters around these issues.

The third component is developing de novo guidances or revising existing guidances in model-informed drug development. These, of course, will be informed by our discussions as part of those stakeholder engagements and workshops.

Also, we intend to revise relevant MAPPs, SOPs, as well as internal training documents and educational documents, as appropriate.

And we look to strengthen staff capacity to support these strategies, both on the regulatory science side as well as on the review side.

The second proposal has to do with biomarker qualification. The need for scientific development and regulatory acceptance of robust biomarkers for a variety of drug development contexts has been very well discussed. This goes back even to the critical path opportunities list.

And qualification, as a formal regulatory program to that end, has been worked out to some extent. This proposal was meant to increase the robustness of that program and provide more framework for facilitating development of these biomarkers from a scientific standpoint.

The idea here is to develop staff capacity to enhance biomarker qualification review in terms of increasing base capacity, so this is one of the essentially unfunded mandates that we've had historically, and this is an opportunity to meet stakeholder needs by creating more critical mass to deal with these issues.

The second piece was to convene public meetings to discuss biomarker qualification both in terms of biomarker taxonomy essentially to get a

vocabulary to get scientists, regulators, drug developers, and others on the same page, as well as to develop evidentiary considerations and constructs for vetting and qualification of biomarkers for use in a variety of settings.

The hope is that these engagements would then be parlayed into guidances both for internal and industry scientists on the biomarker taxonomy as well as the evidentiary considerations, depending on the context for biomarker use. The idea then was or in conjunction is to develop or enhance our current processes related to biomarker qualification.

And the final component is to maintain a public website to communicate biomarker portfolios that are actually going through this formal qualification process both on the consultation and advice side as well as the review side. This would be updated quarterly. We would also post reviews and supporting documents related to these dossiers to both ensure transparency as well as stimulate work in this space.

Thank you.

Terry?

MS. TOIGO: So the last proposal in this group is "Enhancing Use of Real-World Evidence in Regulatory Decision-Making." There has been a lot of discussion about opportunities associated with the use of real-world evidence. And so as our ability to generate and use real-world evidence continues to evolve and grow, it's important that FDA develop methodologies that enable exploration of the possibilities of using this data to evaluate safety and effectiveness.

So to do this is going to require an understanding of what questions we need to ask, including how such data can be generated and how it can be used appropriately in regulatory decision-making. What are the challenges associated with the appropriate generation and use of these data? And then how do we address these challenges?

So the PDUFA resources, as you can see on the slide, are intended to support a public workshop, and then other activities on topics related to addressing the key outstanding concerns and

considerations in the use of real-world evidence for regulatory decision-making.

Stakeholder involvement and feedback will be critical to the success of this project. We and industry agreed to this during the negotiations.

The PDUFA-supported activities will then help inform guidance on how real-world evidence can contribute to the assessment of safety and effectiveness in regulatory submissions. And if you've been following this area, you know that we've already had some public meetings. There was a Duke-Margolis meeting in March, and there have been others where FDA is already talking about this.

But I think one thing I want to leave you with is Drs. Califf and Sherman put out a blog in December when we were in the middle of negotiating this. And I'll read you one part of this.

"The incorporation of real-world evidence, that is, evidence derived from data gathered from actual patient experiences in all their diversity, in many ways, represents an important step toward a fundamentally better understanding of states of

disease and health.

"As we begin to adapt real-world data into our processes for creating scientific evidence, and as we begin to recognize and effectively address their challenges, we are likely to find that the quality of the answers we receive will depend in large part on whether we can frame the questions in a meaningful way."

And I think we talked about that during the negotiation process, and it's still relevant.

So that ends, I think, our presentation. I'll turn it back to Pujita.

MS. VAIDYA: Thank you, everyone.

As before, now I would like to ask our panel of stakeholders to please provide your views on the recommendations. We'll start off with our patient stakeholders followed by our industry stakeholders.

So first I'll turn it over to Maureen.

MS. JAPHA: Great. Thank you. And I would like to thank FDA for the opportunity to participate in this morning's panel.

As I mentioned earlier, my name is Maureen

Japha. I'm the Director of Regulatory Policy at FasterCures and legal counsel for the Milken Institute.

FasterCures is a nonprofit, nonpartisan, DC-based center of the Milken Institute, and we work to bring greater efficiency to the biomedical R&D process across diseases by finding ways to reduce the time it takes to move promising discoveries from the lab to the patients.

Since our inception in 2003, FasterCures has been working to put patients forward as partners in the biomedical research enterprise. To that end, we work closely with our research acceleration and innovation network, or TRAIN group, of over 80 forward-thinking venture philanthropies to advance a number of patient-centric activities.

And, specifically, our Patients Count program was established with the primary goal of seizing new opportunities for patients' perspectives to shape the discovery, development, and delivery of medical products and enhance the science of patient input.

We applaud FDA and industry for the commitment demonstrated in the PDUFA VI goals letter to enhance regulatory science with a specific focus on more effectively integrating patient perspectives into drug development and regulatory decision-making.

My comments here will just highlight on a few aspects of the regulatory decision tools enhancements that were discussed here today.

First, we were very excited to see the commitment to support and enhance the incorporation of the patient's voice into drug development and decision-making and think this will be a really important bridge from patient-focused drug development under PDUFA V to the next step and the next level of really effectively advancing the science of patient input and integrating the patient voice in a meaningful way.

Specifically, we applaud the commitment to strengthen staff capacity to develop and use patient-focused methods. We believe the appropriate expertise was identified there in the commitment letter, but note that it's important to make sure that there is

the appropriate mix of expertise to the task at hand and want to make sure that that's considered throughout the process when filling roles and allocating staff time.

And I know hiring is going to be addressed in the next panel, but I do want to take a moment to just commend FDA and industry for the commitment in allocation of user fees to enhance staff capacity. We think it's hugely important to ensuring that FDA is able to carry out the commitments of PDUFA, and we hope that there will be an ongoing effort to not only hire the right people, but ensure that the right people are working on the right tasks and that they're retained and able to stay on and advance through.

We are pleased to see that the commitment letter specifically identifies the core responsibility of the staff will be to engage patient stakeholders. We think this is a critically important piece and we're pleased to see the explicit direction that that would be a component of the increased staff capacity's role.

We're supportive of the guidance process

that's been laid out in this provision and think these are the appropriate and necessary questions that need to be explored to meaningfully advance the science of patient input and take patient-focused drug development to the next level.

We think the public engagement components of these guidance developments are critical and necessary to ensure that external experts are appropriately engaged and, in particular, that patients are engaged and can weigh in throughout this process.

We understand and recognize the need to include these timelines. Of course, we hope that this can be a process that can move forward even faster than what's outlined there, and we look forward to working with FDA and others to do what we can to make sure this moves forward efficiently and appropriately.

Finally, we applaud FDA's proposal to create the repository of publicly available tools on its website. And as Theresa alluded to in her comments, lots of groups are working on compiling some of these things so we aren't reinventing the wheel. At FasterCures, we have already started to pull together

a list of 90 science of patient input resources, so we hope that that will be a useful resource for not only FDA but others who are working in this phase because we agree that that's really important to make sure we're not duplicating efforts here.

Second, I want to move on to the proposal to enhance benefit-risk assessment in regulatory decision-making. Again, we are supportive of FDA's commitment here to update the Implementation Plan. We support the efforts and applaud their efforts to promote application of the benefit-risk assessment throughout the medical product life cycle, not just at the time of approval.

And we commend the focus on identifying appropriate approaches to communicate to the public FDA's thinking on a products benefit-risk assessment. Too often, patients and others in the public are left in the dark about how FDA reached its decision and have no way of evaluating whether the information they provided had the impact on regulatory decision-making. So we think that this is an important piece and important part of the feedback back to the public.

Finally, we're excited to see the enhancements proposed around the use of real-world evidence in regulatory decision-making. We think this is an area with huge potential for the community as a whole, and patients in particular, and we look forward to working with all stakeholders to explore appropriate uses and applications of real-world evidence.

So again I want to thank FDA for the opportunity to participate today, and we look forward to working with FDA and other stakeholders to move forward in PDUFA VI.

MS. VAIDYA: Thank you, Maureen.

Next we have Marc.

MR. BOUTIN: Good morning, everyone. About a decade ago, there was an author, actually an award-winning journalist and news producer, Richard Cohen, who wrote a book called Blindsided, and it chronicled his plight from going from a severely health person to somebody with MS and colon cancer.

Shortly afterwards, he wrote another book called Strong at the Broken Places, which, for those

of you who may know, is a take from a very well-known author. But Strong at the Broken Places was about five people with chronic diseases that range from Crohn's and colitis to ALS and other conditions. And in the beginning of that book, he says, These are the faces of illness in America. Do not look away. Too often the sick are seen and not heard. Listen. Pay attention.

In many respects, we have made it too easy for people to look away. We don't want to burden you with our disease. We don't want to remind you of the frailty of human health. And for a long time, we let others speak on our behalf, our doctors, academics, researchers. But ironically, they engage with us for a very short percent of our lives, by some estimates, less than .1 percent of our time. The rest of the time we're living our lives experiencing our diseases, taking the treatments.

We have information that is important for the mix. At the end of the PDUFA IV agreement, we decided enough was enough. Surrogates, while critically important, cannot and should not speak on

our behalf. We went to Congress and we said, "We want to have a role in the agreements." Hence, these stakeholder meetings that started with PDUFA V.

And I remember actually having conversations with Theresa -- and I think, Patrick, you were involved in some of these conversations -- when you had to engage the patient and consumer community. I suspect you thought, "Oh, my god, what are we going to have to do?" This is a group of people that are emotive, high charged, they don't have data, but to FDA's credit, they listened, they paid attention.

In PDUFA V, we saw a number of things that the patient community advocated for, the benefit-risk framework. We saw resources go to biomarkers and patient-reported outcomes and rare disease. We also saw what became the emergence of the Patient-Focused Drug Development Program, and many thought that was just a complete waste of time.

And yet with those meetings, we've had people come in and explain the burden of disease, the burden of treatment, and in every instance, people have walked away saying, "What I thought was most

important, what we heard from surrogates, was not what was most important to the patient."

And now we recognize that we need to mine this information, we need to turn it into data, as Theresa said earlier, and we need to incorporate it not just in regulatory review, but in how we develop drugs.

And now everyone in the biopharmaceutical sector is looking at how they incorporate this into the development of their products. It will lead to higher valued treatments that respond to the issues that are important to people with chronic diseases and disabilities.

When you look at what we have in PDUFA VI, a large number of regulatory decision tools, think about how difficult it is for an agency to look at new tools and figure out to incorporate them when they are charged with ensuring safety and efficacy. Think of the challenge for the biopharmaceutical sector when they would like to develop and deploy these tools, but there's no regulatory certainty or predictability on how to do it. Why would you invest? Why would you

put the money there?

What FDA and industry have done is they have laid out a map that ends that juggernaut, that catch-22, of, how do you move forward with 21st century science and develop and utilize these tools in a way that will produce higher value products, faster, safer, more tailored to individual subpopulations?

When you look at the incorporation of the patient voice and the guidances that have been laid out, that will provide the clarity so that not a single company is going to develop a product without engaging the end user throughout that development. That's going to lead to higher value products, and that content is going to be pulled forward into the delivery system in ways that we can't even imagine, but it will have huge impacts on ensuring that people get the right treatment at the right time, huge opportunities.

It's integration into the benefit-risk decision-making. What an amazing opportunity.

I've been in this room and I've hit the table with my fist saying, "You need to ensure that

your benefit-risk determinations reflect the end user."

We now are setting up the mechanism so that we can, in a representative, validated way, capture that data and incorporate it and communicate it in how benefit-risk determinations are made. How significant is that?

Real-world evidence, already addressed, but you know what? I understand the challenge with this, and there are a lot of issues. We don't yet know exactly how to do this, but I will tell you, if you went to 133 million people who are now living with one or more chronic diseases and said, "Do you know what real-world evidence is?" they would be able to give you a pretty good sense of what it actually is. They won't know all the nuances, but they'll understand it.

And then if you were to tell them, "We don't use it in drug development," you would have some people with really serious life-threatening diseases and parents with those conditions who would be really pretty upset.

It's time to figure out, how do we

incorporate this information? Especially for the vast majority of people who have multiple chronic conditions, which is rarely incorporated in clinical trial design. Having that information will make this far more safe, and it will us opportunities to find other options for these treatments beyond simply using products off-label.

Adaptive clinical trial designs. From a patient perspective, for so many patients, especially children, in particular, children with rare disease, they get one shot at a clinical trial, and then their life is likely over, or they may not have an opportunity to participate in another.

If you're in a standard randomized clinical trial and you're in the wrong arm, you've lost your one opportunity. The science is there. We can do better. We need to stand up and figure out how to do it.

Model-informed drug development. What a huge opportunity to mitigate the risks and harm associated with participating in clinical trials, helping to make the process faster, to bring safe,

effective treatments to market.

Biomarkers, surrogate endpoints, already discussed.

I want to add my thanks to the FDA and industry. You didn't look away, you heard us, you paid attention. We want to work with you to implement PDUFA VI.

Thank you.

MS. VAIDYA: Thank you, Marc.

Next we have Annie.

MS. KENNEDY: Hi. Good morning, almost afternoon. I'm Annie Kennedy. I'm with Parent Project Muscular Dystrophy. And since you're in this room and in this space, you're probably familiar about the context for the Duchenne community and what's been going on in the last 5 years, but especially the last year, since our negotiations and discussions around PDUFA VI first began.

And I would like to thank the Agency for the really solid engagement around PDUFA VI. And I would like to thank BIO and PhRMA for engaging the patient community and coming back to us in an ongoing way to

have a clear understanding of what we were concerned about going into PDUFA VI.

In the last 5 years, we have really considered PDUFA V to be a very solid framework, which became very foundational for our community and so many communities, and we really embraced the Patient-Focused Drug Development charge, if you will, and became early adopters of that charge.

PPMD was one of the first organizations to convene a meeting. We were not 1 of the 20 on the list, Duchenne was not selected, but we held our own, convened our own, meeting in cooperation with the FDA, which was a very successful meeting and laid the groundwork for the development of a community-led guidance at the invitation of the FDA. FDA, 11 months later, turned around and issued the Duchenne guidance for industry.

We have published already two benefit-risk documents or patient preference surveys and are in the process of a third, and we have incorporated a PRO into our registry.

So PFDD tools are real-time and incredibly

important to our patient community. And since last July, since these discussions have happened, we have had two advisory committee meetings for two product reviews, and a third product has received an RTF, which in our community, we did not even know what that acronym stood for initially, and we are now very well aware of what that is and what the process between the FDA and the industry sponsor is.

So we have literally been flying the plane while building it and sometimes felt like there was a jet flying by the tower for our patient community. And this a patient community with a significant unmet medical need and a robust pipeline that we feel cannot be chilled, and we must continue to incentivize industry to be working in our space.

So when we saw the commitment letter, we were thrilled, we must say. We felt that the interactions that we had had in I don't know how many meetings, I feel like we've had seven meetings here, but that could be my hallucinating, but we've had a lot of interactions, there have been a lot of comments submitted. We felt that we had been heard.

With that being said, since the ink isn't dry, and we feel that there could be a few enhancements -- and I will say I feel like I'm sitting on a trap door, so if there's a button, Theresa, over there, you can feel free to open it at any moment.

But there are a few elements of the regulatory decision-making that are particularly important to us, and we feel that there could be a few enhancements that would be in line with the commitment that the Agency is making that would really speak to what's happening in real time in many of our communities right now.

So one of them relates to one of the things that we were most pleased to see was the commitment from the Agency around guidance development in the stakeholder engagement, the PFDD sector. We are delighted to see that that will be happening.

We're also delighted to see the format for that, that there will be engagement with stakeholders followed by then the development of the guidances.

What we're concerned about is the timeline for such a process. We understand that that's a

tedious process and there's a delicate dance in promoting a nascent field and the type of oversight that's necessary.

But what we're concerned about is that there are products currently in review for which there are disease-specific PFDD tools with methodological rigor currently available, and that those timelines will not match up necessarily. And we're concerned that the current development of additional tools could be delayed, chilled, slowed.

So what we are requesting is that the Agency consider issuance of best practices in the form of interim guidance so that we could continue to incentivize development while the stakeholder engagement and the eventual draft guidance comes out.

Another area that's incredibly important to us is benefit-risk. As I said, we have already conducted two benefit-risk studies, or patient preference studies. We have a third underway.

PPMD and BIO collaborated on recommendations to send some recommendations to the field. We worked with some of the experts in the field to put this

forward, and they were published in June. They can be found on BIO's website or PPMD's website.

But we now, as I said, have had two advisory committee meetings conducted for products in Duchenne, and in neither of those meetings was the benefit-risk matrix completed. So what we're proposing is a refinement of the proposed performance goals such that the Agency commit to completing a benefit-risk evaluation for every candidate therapy that would address an unmet medical need.

Even in cases where the Agency may question the overall benefit or efficacy of the candidate therapy, if this is the case, such perspectives should be noted within the review, but this would enable the Agency to put forward the benefit-risk evaluation.

And then the last enhancement or modification or tweak in this -- again, the trap door is under me -- is what we would refer to as regulatory communication. So we would encourage that the FDA and industry together consider ways to enhance the regulatory communication processes, especially when a PDUFA date deadline has lapsed.

The Duchenne community right now is in the midst of such a scenario, and when that happens, there is a lack of official information, and that creates a void which yields frustration and angst in the community. And as we all know, that's not good for the patient community, it's not good for the sponsor, it's not good for the FDA, it's not good for any stakeholder.

And we appreciate the complexity of any review that goes past the PDUFA deadline, and that there is a commitment from all parties to conduct a thorough review as quickly as possible. But what we would ask be considered is that the Agency consider the merits of issuing a brief update 30 days following a PDUFA deadline and every day 30 days thereafter, so 30 days after the PDUFA deadline and every 30 days thereafter, until the Agency issues an approval or a complete response letter. We believe that such a cycle would extend the commitment to enhance communications that's included in the draft performance goals.

Again, we thank you for this opportunity

today and for the ongoing communications.

MS. VAIDYA: Okay. Thank you, Annie.

And next we have Ian.

MR. KREMER: Good morning again, everybody. And I'll just add our thanks on behalf of the LEAD Coalition both to industry and the FDA as well as to the broader stakeholder community for everything that has led up to this commitment letter.

We have, as I said earlier, 90 member organizations and another 60 or so that we are informally aligned with. And I don't know that I'm in a position to embrace every word within the commitment letter on behalf of that wide and diverse a set of stakeholders. I can say generally there is a warm embrace, but I'll leave it to those individual organizations for their specific recommendations about words they would have changed or added.

With that, I think all of us would embrace making sure that the words "staff capacity" appear on every slide where they may have accidentally been omitted. That's going to be the end game. It's about implementation.

I think what you've got is a package of recommendations that are incredibly strong by and large, certainly subject to a little bit of tweaking here and there, and in some organizations, may be a lot of tweaking, but you can't make any of it real, you can't get it off the page, without the staff capacity.

So I hope, at a minimum, there is consensus around the need for driving as much resource as possible into actualizing the wonderful and robust ideas and giving the Agency the ability to be even more robust about future ideas.

So with that, I'm going to focus most of my time -- I think you said 15 minutes? -- on implementation and why this is going to be really, really hard, and I'm going to sound a little bit like a broken record. And I'll own the fact that I only know about two things in this world, dementia and my son's college application process. So feel free to ask me questions about either of those later.

I'm going to put this all in the context of dementia and people living with various causes of

dementia and at different stages of dementia, but I hope that those of you from other patient advocacy communities will hear something that resonates for your community in at least some of the examples. So I'm going to run through these pretty quickly, about 20 seconds each.

First, embracing what Marc said about there is no substitute for the patient voice. Completely true in the dementia community, but we know there also has to be a place and a role for the caregivers, however defined. And if you prefer to call them care partners, carers, use the nomenclature you prefer, but their voice matters, too, not instead, not more, but also.

In terms of benefit-risk analysis, incredibly important, incredibly complex. I would just say that at least again in our community, and I suspect in a number of others, something that makes it all that much harder is that those attitudes about benefit and risk change with different stages of dementia. And pivoting into the next point, it also depends on what kind of dementia you have, what its

source is, what its manifestations are.

So Alzheimer's is one of literally a hundred different disorders and diseases that cause an umbrella set of symptoms that we call dementia, but it plays out very differently depending on the organic cause, what the disease or the disorder is. And so your benefits and your risks are going to vary enormously, too.

It is not adequate for FDA or industry to say, "We had a bunch of people with dementia," or to say, "We had a bunch of people with Alzheimer's." It won't be representative. And we're going to need to make sure that it's the right set of patients and the right set of carers and other experts that are opining on the benefit-risk analysis based on disease.

It's also going to matter in terms of the age of onset. So you have people with dementia who -- kind of the stereotypical person with Alzheimer's who's in their seventies or eighties. You have a tremendous number of people, varying estimates in this country would say about a quarter of a million give or take, who are under age 65.

In addition, you have a wide number of people with intellectual and developmental disabilities, primarily, but not only, Down syndrome, who acquire symptoms of either Alzheimer's or another one of the causes of dementia. Their world views are necessarily and appropriately going to be different, and we need to take that into account.

I won't repeat what Marc and others have said about comorbid conditions, but that certainly is an accelerant to the challenges of both obtaining and interpreting the responses that one would get.

I would also add that we know there are chronic problems in this country in terms of clinical trial recruitment, but also in terms of acquiring and analyzing patient and care review point in terms of underrepresentation of communities of color.

And I would add -- and I apologize because I have zero data for this, it's just raw speculation on my part -- I bet you anything that we're also underrepresenting people in rural communities, and their benefit and risk analysis are going to be different, not least of all because of their access to

the therapies that we would like them to have access to.

So it's not just, Can they get a prescription? It's, Can they maintain the medication management regimen that's necessary, and what will that do to their benefit-risk analysis?

A few more points I would like to make, but I know we're really limited on time, so I'll put a few of these in writing for Theresa, but the last one I want to focus on is stigma. Across a lot of disease states, stigma is an enormous issue. I don't know if there is one that has more stigma remaining than dementia. Probably someone could make a good case, and I'm happy to have that conversation, but we're way up there.

So finding people who are willing to be part of FDA's and industry's process of identifying benefit-risk and hearing the true patient voice is compromised by the enormity of the stigma for people to get diagnosed in the first place, to get a differential diagnosis in the second place. So there are a lot of folks who say they have Alzheimer's, they

in fact don't, they have another one of the diseases or disorders, but they haven't either had access to or been willing to pursue a differential diagnosis.

And then, third, even if they've got that differential diagnosis, their ability to speak and their willingness to speak for others who are also stigmatized, that is an enormous lift that you are asking people to make as individuals on behalf of a wider population.

So our work and part of where that staff capacity has to go is creating a fundamentally different environment in which patients and carers are willing to come forward and are able to come forward in a way that is genuinely representative. That weight can't all be on their shoulders as individuals, that's on all of us working collectively.

MS. VAIDYA: Thank you, Ian.

Next we have Sascha.

DR. HAVEFIELD: Thank you. And I'll keep it very brief. Like the provisions covered under the first panel, we are fully supportive of these drug development tools provisions, as our continued ability

to integrate 21st century science and keep pace with medical and scientific innovation is essential to the success of the Human Drug Review Program.

PDUFA VI will be critical to the integration of innovative regulatory science approaches into drug development and review, including advancing the science of patient input, as we just covered here now, facilitating the use of novel trial designs, supporting the use of drug development tools, biomarkers, patient-reported outcomes, model-informed drug development, and the use of real-world evidence for regulatory decision-making.

So I'll go into a couple more highlights here: enhancing the patient voice, facilitating the development and application of scientific methods, that is, that incorporate the patient perspective into drug development, is our highest priority and is critical to our ability to ensure that medicines better reflect measures that are meaningful to patients.

Innovative clinical trial designs. Innovative clinical trial design approaches have the

potential to enhance the efficiency of drug development and regulatory review, as we just heard, and help accelerate patient access to safe and effective new medicines, very important from our perspective.

Model-informed drug development, MIDD, and related statistical and modeling approaches also have the potential to focus preclinical and clinical studies, avoid unnecessary exposures, as we heard before, enhance the quality of the data, and ultimately accelerate the development and availability of innovative medicines.

Qualification of pathways for biomarkers, drug development tools, including biomarkers -- Maureen, you highlighted this great promise for advancing drug discovery and accelerating the development of new medicines for patients.

With PDUFA VI increasing staff capacity and resources for the qualification of biomarkers, including piloting the approaches to engage external experts and FDA's qualification process, I think this is a major step forward. The same or in addition,

PDUFA VI will establish, as we heard, a dedicated process for scientific consultation between the Agency and drug developers for drug development programs that plan to use a biomarker as a novel surrogate endpoint, and these provisions go hand-in-hand.

And last, but not least, real-world evidence can be, and is, a valuable source of information about the safety and effectiveness of medicines in the broader population beyond that studied in clinical trials.

As you heard from Terry and in the quote from Dr. Califf, RWE is any data on the use, benefits, and risks of medicine that is derived other than from randomized clinical trials. And PDUFA VI will explore the potential use of real-world evidence for regulatory decision-making through public workshops with key stakeholders, pilot studies, and ultimately, and that is important, the publication of guidance on how RWE can contribute to the assessment of the safety and effectiveness of medicines.

Thank you again, and turning it back to you.

MS. VAIDYA: Thank you, Sascha.

And, finally, we have Kay.

MS. HOLCOMBE: Finally we have Kay.

(Laughter.)

MS. HOLCOMBE: And when you're the last person, you can be really brief because everything already has been said. But Sascha noted that it was PhRMA's top priority and it was also BIO's top priority to deal with the issue of hearing, listening to, and incorporating the patient voice into all of our decisions through the drug development process.

I think when we think about PDUFA, we often focus only at the very end, i.e., what is the job that FDA is doing? But really, it's the tip of the iceberg, is it not? FDA takes 5 minutes to make its decision, and we take 15 years to get them something on which to make a decision.

So building all of these concepts into the notion that it takes a really long time to develop a drug, and it costs a really lot of patient time and money to get to the point even where you have an application to submit to FDA makes all of these things so important to getting our goal accomplished of

getting therapy to the patient in a timely way.

So incorporating the patient voice means incorporating it throughout the process so that we in the industry listen to patients and understand what it is that they need and what they want

We cannot develop drugs anymore by simply deciding, "Wow, this is a great idea, we're going to put this drug out there and we hope a lot of people will buy it," because that is not going to work. We need to understand what it is that patients really need, and we need to listen to them. And we believe that we are going to learn as much from these guidances that FDA will be developing and these public processes that are going to go into doing these guidances as much as FDA will learn.

We also think that this patient-focused drug development activity is inextricably linked to the benefit-risk decision. It is crucially important that we look at this as one continuous process, understand the disease from the perspective of the person who has the disease, understand the therapy and the benefits and the risks of that therapy from the patient's

perspective and incorporate that knowledge, which, because of FDA's work in PDUFA VI, will now be much more science-based, and we will be able to validate that information, incorporate that into the regulatory decision, and importantly for all patients and caregivers and providers, get that information on the drug label. We cannot put anecdotes on the drug label.

So this is all a way for us to convert what always has been an anecdote into real data that can be on the label and help people use this therapy in the way that is the safest and most effective for each individual patient.

So I feel pretty strongly about this, so I'm going to move on to something that -- I want to say a few words about innovative trial design, not because I understand what it means, so I just want to make that clear. So of the 150 people who get their Ph.D. in biostat every year, I am not one of those people, so just putting that out there.

So we asked our companies, when everybody wanted to talk to FDA in PDUFA VI about innovative

trial design except they always want to talk about adaptive trial design, and then they wanted to talk about Bayesian statistics. Really, really.

So we asked them after this PDUFA VI agreement, we asked our companies, "What is it that we really need to get out of this? This pilot project is a great idea. It's going to allow companies to bring in creative ways of doing trials -- by "creative" -- Lisa is getting nervous about the word "creative" -- I mean like statistically okay ones.

(Laughter.)

MS. HOLCOMBE: But they're going to bring these ideas in. FDA is going to work with them on how to implement those ideas, this innovative design, and then talk about this publicly about what kinds of designs are okay and what kinds haven't turned out so well. What is it that we think has been the problem, and are we going to solve it here?

And the number one thing that we heard -- and John Jenkins is not going to be shocked by my saying this -- is that we don't have a consistent response by FDA review divisions when we go in there

to talk to them about these really frightening, awful things like Bayesian statistics.

And so what we would like to see is for kind of everybody to get on the right ship here and have these conversations in a way that levels the playing field regardless of which therapeutic area in which you are working. And I think we have a great start on doing that by this PDUFA VI agreement and these pilot programs.

And we are very hopeful, and we are encouraging, and I know PhRMA is as well, all of our companies to think seriously about participating in these pilot studies because we all are going to learn from each other, and this will lift all boats, to use a really awful cliché.

And, finally, I just want to say a word about real-world evidence. I did say a word about it talking about Sentinel, which is like the biggest source of real-world evidence the world will ever know.

But we are very interested, and we talked with FDA throughout this process, about whether, how,

and in what context can we use all of this information that is out there in the real world about how patients have turned out after using therapies that are on the market to look at the question of effectiveness as well as to look at questions that we are already looking at in Sentinel, which is questions of signals of safety problems that we were not able to see in our clinical trials.

And effectiveness, for example, for a new indication of an already marketed product. Is there information out there by patient and provider use of this product that would be helpful to us in getting a new indication on the label of the drug as opposed to just an indication for which doctors are using this drug, but we don't have it on the label? So it disadvantages all doctors who are just operating based on reading the label, which a lot of them aren't doing anyway.

So in short and in brief and in summary, I want to go back to this notion of this PDUFA's focus on drug development. This is about getting the patient access to a safe and effective product by what

we all do collectively from the moment we have the good idea till the moment that good idea finally reaches the doorstep of the FDA, and these agreements are going to help that process be more efficient, and that efficiency will be good for patients.

MS. VAIDYA: Thank you, Kay.

And I would like to turn it to Theresa for final comments.

DR. MULLIN: Thank you. I just want to respond a little bit to some of the things that Annie mentioned, and I think it's something that maybe it's a point that needs to be made to be clearer for everyone. And so a couple of things.

The first one I think she mentioned was a concern about the timeline for those guidances. And I want to go back. And I really appreciate, practically everyone up here said that they wanted us to have more resources and more staff, and they understood we need more staff capacity.

Well, we thought very hard about the guidelines and the guidances, I should say, and what you need to keep in mind is that when I said a handful

of people, I meant five. Okay? I meant five, and only three of those really are experienced enough that they could work on a guidance. And then we've got the other folks, and there are maybe three or four over there that are experienced enough that they could write a guidance document that you would then take and stake your whole program on. You can't just hand that to the newest person who walks in the door.

Now, both of these staffs, the staffs who do this work -- and let me tell you, the patient area right now, as you probably all know, is very hot, it's very hard to hire anybody, and, in fact, when we let our people go to conferences, we do let them go out, we let them out sometimes -- they are showered with job offers to make two and three times what we can pay them and have more flexibility with their hours.

So you can imagine why we think we -- we sign the agreement, we let them go every time, but it's always with a little bit of a choke in our throat about letting them go to these conferences. But that's the situation, folks. Okay? We're talking about very few people who could have the expertise to

write the guidance. And we don't want to kill them.

And we also want them to keep doing work, like you said. There are people developing drugs right now. We don't want to take them offline and let them not talk to patients so they can go work on these guidances; we want them to keep reviewing what's coming in.

So our compromise is to spread this out so we can still be helping sponsors and patient groups who want to come in tomorrow, and they're working on stuff today, do that, balance that, with hiring, trying to hire, because these people also have to help us hire other people like them, and to do this guidance work.

So it's definitely a compromise, but that's the reality. When we talk about not having enough staff capacity, it means we don't have enough capacity to do this stuff we're talking about. So we have to both do it, write the guidances, and do all these other things.

And that's why the work is spread out, because writing guidances that are good is

non-trivial. Okay? It's not something you can, "Oh, I just needed to take my weekend and do it." It's not like that. This is really hard to write. And this is stuff if it had been that easy, we would have written it already.

So that's one of the reasons. I mean, we're a little bit frustrated by all these things, too, but that's why this stuff is spread out over several years. And, of course, that is longer than any of us would like it to be, but that's why it is.

And the good news also to tell you is that we are completing that benefit-risk framework for all of our regulatory decisions related to drug applications. Now, we don't make them public for applications that are not approved, just like we don't make the rest of the information available for applications that are not approved.

And the other thing I'll say is please be careful when you have a frustration with not knowing what's going on in a particular case to generalize that into a reporting requirement that will then apply to everyone in every instance because there is nothing

that will eat up the few resources we have faster than getting another reporting requirement imposed on us.

So please think about that, that these are the same people that are doing the reviews are going to be having to do that. So that's the other thing I'll just say because staff capacity is our most crying issue. And in our next panel, we'll talk a little bit more about what we're committing to in this effort to try to help with that.

Thanks.

MS. VAIDYA: Thank you, Theresa.

And I would like to thank all of our panelists here today.

So now we will be taking a lunch break and reconvening at 12:25. Thank you.

(Lunch.)

Panel 3 -- Administrative Enhancements: Hiring, IT, and Financial

MS. VAIDYA: Panelists, please come up to the front and take their seats.

Okay. Great. Well, I hope you all had a great lunch. I know it was a little short, but just

trying to stay on schedule here today.

So now we will begin our last panel session today, on administrative enhancements, which includes hiring, IT, and financial.

First, I would like our panelists to please introduce themselves because we do have some new faces here. So I'll start off with Brad.

MR. WINTERMUTE: Hi. My name is Brad Wintermute. I am the Deputy CIO here. And I was the lead for the informatics, which covers the electronics submission and data standards for the PDUFA VI.

MR. KISH: Hi. I'm Andy Kish, in CDER, and I was the lead for the financial negotiations.

DR. MULLIN: Theresa Mullin, Director of the Office of Strategic Programs in CDER. I'm going to talk about hiring.

MS. MARCHIBRODA: Hello. Janet Marchibroda, Director of Health Innovation at the Bipartisan Policy Center.

MS. BENS: Good afternoon, everybody. I'm Cynthia Bens, Vice President of Public Policy at the Alliance for Aging Research.

DR. ALLEN: Hi. Jeff Allen, Executive Director, Friends of Cancer Research.

DR. HAVEFIELD: Sascha Havefield, for PhRMA.

MS. HOLCOMBE: Kay Holcombe.

MS. VAIDYA: Okay. Well, thank you. And now I'll turn the mike over to Brad, who will be talking about some of the IT commitments.

MR. WINTERMUTE: So from an IT perspective, we focused on electronic submission process because, as you all know, the ability to transmit data into the FDA using electronic means is very important from a sponsor perspective but also from an FDA perspective. We want that data to come in, in a standard format that we can then disseminate efficiently for effectively utilizing the data through our review process.

So one of the areas we focused on was the actual submission process and then the tool sets that we're using in that. When we look at it from a standpoint of 5 years starting in the fall of '17, it's kind of hard to predict where IT is going to go. If you think about what's happened in the last 5 years

in your personal life from an IT perspective, you're probably using ways now that you never used before.

So we tried, as you'll see through this, put in place mechanisms to solicit feedback and adapt as we go through, which I think will really be good to allow us to keep up with the pace of technology.

So the first thing we're going to do is make sure that we publish and maintain electronic submission documentation, include description of all the processes and milestones and everything, and the rejection process that happens as it goes through its validation when we get a submission in. That way it's very clear and transparent as far as what the process is.

We're going to publish targets for and measure basically availability, especially during business hours, availability. So we've deemed a business hour window, and we're going to focus on high availability for sure during that window period to make sure that any maintenance that we do to the system, Electronic System Gateway, which for those of you who might not know, is our gateway into the FDA

through electronic submitting, we'll do any kind of maintenance that we need to do outside of regular business hours, which we tend to do today anyway, it would just formalize that process.

We will publish target timeframes for expected submission upload duration and then the timeframe between key milestones and notifications that happen during that submission process. And so that will allow industry to have a better understanding of how long something should take. So if it's supposed to take 30 minutes, and it's taken 4 hours, maybe there is some issue there.

We'll also implement ability to communicate electronic submission milestone notifications to a sender or designated contact. Today it kind of goes back to whoever sent it, and sometimes they want to have an alternative, from a notification perspective, in case somebody is on vacation or something like that.

And then we'll document and implement a process to provide ample notification for system changes, especially where a user interfaces update

happens. So if we're just doing something on the back end, that would be just notification that we may be having a system go down for a short period of time while we do an upgrade, but if we're doing something that's going to change either the way you're doing submissions or a user interface that you've having to interact with, we'll make sure we give you plenty of notification to communicate to your staff and make sure that the industry can train staff as appropriate.

Continuing on, also here the opportunity was for transparency and communication around the submission and the data standards. So we want to make sure -- this is part of what I talked about -- kind of having a two-way dialog and communication as we go on, as planned, and hold quarterly meetings to share performance updates between FDA and industry so we can understand what's happening in the environment.

In an annual meeting then, also seek stakeholder input for past performance, future targets, emerging industry needs, and technology initiatives. So basically, what are we seeing? What are the realities? We see from our side what the

response is. What is industry seeing and what are they predicting from a future perspective? This allows us to make adaptations as we go forward.

And then we'll also post historic and current metrics so that you can see trends. This will help us from an analysis perspective so that we can see -- you know, one of the concerns I had was the size of submissions continues to get larger as we use things like genomic sequencing, et cetera. What is that trend going to be and how are we maintaining pace with, say, either additional volume in submissions or size, actual physical size?

So this gives us the ability to take a look at that and say, yeah, we've seen the increases go up, but we're also still processing within a timeframe that makes sense. So that will be something that we publish.

We'll also incorporate strategic initiatives for the PDUFA goals into our overall IT strategic plan. This was kind of an administrative reduction, if you will, of duplicate efforts.

We currently have an IT strategic plan.

It's available on our FDA.gov website. I encourage everybody to take a look at that. We also separately do a PDUFA IT plan. And really it should be one and the same. What we do overall from an IT perspective needs to support PDUFA and all the other UFAs and non-UFA stuff. Right? So we're going to make sure that we incorporate a section into the IT plan for PDUFA specifically but not necessarily do a separate plan for PDUFA.

And, again, that's a reduction in extra effort that really didn't gain anything. You'll have it in the overall plan, and you'll see it in context of the overall.

We'll also continue to collaborate with standards development organizations and stakeholders to ensure long-term stability on standards, like ECTD, et cetera. And really what we're doing here is making sure that we're maintaining what's happening, we're communicating properly, just as we do today, into the future.

Data standards is critical, again, as I kind of mentioned in my opening remark, to get the data

into the FDA and then be able to parse through it efficiently to get the right data to the right person at the right time to make their job go smoother. It's certainly important that data standards has a very key part to play in that whole process. So we'll continue to do the support that we do today on standards and evolve again as we go over the next really 6 years.

I think that's it.

DR. MULLIN: Okay. Well, I think we've established this morning that the staff to do the work is really critical for us to get this done. So what are we going to do?

This is the first time that we've actually put something in the commitment letter related to this administrative function, and we thought making commitments specifically in the letter has been so helpful in helping us focus and get things done and get things fixed in the scientific review areas that we would try the same approach in some of our administrative areas, which are the other critical sort of three legs of the stool.

I mean, we have to have the people, we have

to have the financial systems, we've got to have the processes and the science, and so we're kind of paying attention to the rest of this needed process.

So here is the opportunity I think we all recognize, which is that we have to hire and retain these qualified people. And FDA is a bit unique or maybe an odd duck, if you will, almost in government with having industries that are directly competing for the same kinds of skills. And, in fact, if you have regulatory experience, it might even make you more attractive in some other areas.

And we're working with the federal pay structure and all the rules that are important around the federal workforce and regulations associated with that, but they also create some challenges.

And also I have to say we've had a somewhat underresourced system in place, and it's just modernizing it and trying to bring it into the 21st century is part of what we're trying to do here.

So here is what we proposed as part of this approach to enhance our capacity to recruit and retain and provide a really attractive workplace for those

who really would like to serve the public and come and work here.

First, modernizing the hiring system. Well, what do we mean by that? In the government, you have positions, and there is a position description for every position. But, as Dr. Califf pointed out, I can't remember actually the number, but I think he said something like -- now, please don't quote me back there from the pink sheet because I might get this wrong -- but 20,000 different position descriptions were written up throughout FDA, not just the drug program -- it's okay, Janet, but all of FDA -- and that we surely don't need that many.

So part of this is to modernize and standardize the position descriptions and put them in a database of well-classified robust descriptions so that we can pull those off and not have to go through a classification process every time to make sure you've got the position that you need in order to start the hiring process. So that's pretty basic.

Also, part of this infrastructure -- and I know Brad and company are helping with this as well --

is trying to put in place an informatics support base for this so that they can track the process of hiring. There are many steps in the federal hiring process, and a system that can kind of go end-to-end and follow that step and who's doing what and when are they going to have it done by, the kind of things we would, of course, do in our review processes, we would put in place for hiring as well. So that's what that first item is.

The next one is we have a limited number of folks -- hiring people also have trouble hiring for themselves, so augmenting the HR capacity that we have to do that work, to basically go through all the steps of processing applications and creating certificates of eligibles and this kind of stuff by having contract support for this.

There are people who have experience with federal hiring who we can bring in on contracts. So that's augmenting that capacity so we have extra bandwidth to do this, because we have a lot of hires we would like to -- we're in the fortunate position of being able to make a lot of hires. So that's what we

hope to do to support that.

Next, this is to address -- establish a dedicated function and a unit. This would be in the Office of Medical Products and Tobacco for recruiting and retaining scientific staff, and by that, we mean a set of people who really know the kinds of skill sets we're looking for and can be going to the conferences, knowing when they're going to take place, know where the best places to sort of find the best qualified people for the work we're looking at.

They understand the kind of business we're doing, and they can target and help us, let people know there are these opportunities. You know, not everybody looks at USAJOBS all the time. That's one of the things we learned during this process. It's just like the Federal Register, which you might think we thought we widely read.

(Laughter.)

DR. MULLIN: You know, USAJOBS is also not looked at by a lot of people. So that's where you've got to go to apply for a lot of these jobs in many cases. So having people even be aware that we're

looking is part of what we need to do here, and have the right people know that we're looking who have the skills that we actually need to bring in and do this work.

The next one is a standard user fee kind of idea, which is let's set some clear metrics and goals. And if you looked at the commitment letter, you will see that we have spread it out realistically over 5 years because that's a fair number of hires for us to find the right people and go through this process each year, but specific targets for the numbers of staff.

And those staff, backed out behind that are the offices and the skill sets that match what you've seen in the commitment letter where we say additional capacity is needed, that's what that rolls up into, are those numbers over time, that we think are achievable.

And, finally, something that we did in the new molecular entity review program, which was very helpful, we had a comprehensive continuous assessment of that program, because it was different and it was something we hadn't done before.

So we've put in place something very analogous here for the hiring process. We have a lot of new components that we're looking at here of process innovations we're trying to do.

And what this comprehensive continuous assessment would do, in fact, we've already awarded a contract, we've already gone through the procurement process for this to get this underway, because the initial assessment has to be done very, very early in PDUFA VI, so the work had to start really this summer.

So we've awarded that contract, and that work has begun, and it begins with looking at the capabilities, both in the Office of Human Resources, which is in the Office of Headquarters, and the corresponding components in the centers, and the hiring offices, looking at the whole system, if you will, of hiring that's involved in the Human Drug Review Program, the capabilities, what procedures do people have in place? how are they trained? the policies and practices, and looking at this whole system of interactions and how it's working.

An initial assessment will be done with some

recommendations where the contractor sees the need, and there will be an interim assessment and then a final assessment, and there will be public meetings around, and these reports will be public as well.

So that's it. But this is all really kind of revolutionary for us in the HR area, in the hiring area, so it's very exciting and we're looking forward to it.

With that, I'll pass it along to a very critical part of this whole thing, which is the financial management component of the program, and Andy will talk to you about that.

MR. KISH: So I know this is the topic everyone is most interested in, and you're all steeped in the nuances of PDUFA finances and the statutes, but if you can bear with me, I'll go through the highlights.

Also, as Theresa mentioned, where this was the first time we focused on something administrative like hiring, this is the same case where we took a thorough look at finances to see what is working well and what could be improved. And in a very

collaborative manner, we came up with what we think are some really good improvements and some changes to the fee structure and how it works.

So I'll start with focusing on enhancing the management of PDUFA resources, a theme that ran throughout the entire negotiation that we shared across the table really. Something we did agree to is establishing a capacity planning function utilizing modernized time reporting, capturing where people are spending their time.

For those of you that are familiar with capacity planning, it's something that's quite common in large private sector organizations where it's really a precise accounting of where people are spending their time and how much it costs and then also predicting where your workload is and funding to what that prediction may be.

Also, a thorough look at financial transparency and efficiency. We'll bring in third-party assessment to evaluate the financial administration of the PDUFA program just to get some ideas from external folks about how we can do things a

little bit better, where we can make some improvements.

Also be publishing a PDUFA 5-year financial plan. For those of you who may have paid attention to this in the past, we used to publish it, then we stopped, so we're going to start doing it again. We'll be making updates to that plan every year.

We'll also be convening public meetings each fiscal year starting FY19 to discuss the 5-year financial plan. So if you look at something and you find it very interesting, please come talk to us in the public meeting. We'll also be talking about our progress and implementing modernized time reporting and capacity planning.

The really three key themes that also were discussed thoroughly during negotiations. One was, How can we enhance financial predictability? That's really important to us. And stability and also the efficiency of the program.

As Theresa mentioned, the challenges with hiring, it can sometimes, in my personal experience with staff, take a year to get someone on board. When

you don't have financial predictability for multiple years, you can see the implications there for staffing up.

So we took a look at the current fee structure target revenue allocations, the fee adjustment methodologies, and we saw that it does create some unpredictability year to year in our funding levels. Also in what sponsors pay and what their fee burden is year to year.

It also introduces inefficiency for FDA and industry in some fee administration and payments, some of the structure that we are proposing the change, and this ultimately hinders our ability to engage in long-term financial plans, where we want to be in the long term, and we're looking at PDUFA VI as making that transition.

Some modifications that we're proposing is a change to the fee structure and target revenue allocation, so proposing to shift a greater portion of the target revenue allocation to more predictable fee-paying types. If you're familiar with it now, folks submit applications pay, supplements pay. There is an

establishment fee and a product fee.

Applications and supplements are variable year to year. That funding source is variable, and that adds to unpredictability. So we're looking to discontinue the supplement fee to remove some of that unpredictability, we'll modify the target revenue allocation applications where we're not deriving a third of our target revenue to 20 percent.

And then we are introducing what we're calling the PDUFA program fee, which is really the product fee with some modifications. We'll be deriving 80 percent of our revenue from the product fee. This is a very predictable fee payer year to year, so it really allows us to enhance our long-term financial planning.

Another improvement is discontinuing the establishment fee, which is administratively quite complex to administer, and burdensome. And I know there may be some thoughts out there that establishments actually pay this fee. They don't. That's a misconception that's been out there for a while. It's really the sponsors, the same people that

pay your product fee and your application fee, they pay the establishment fees, so we saw this as an enhancement to the program to discontinuing it.

Modifying the program fee billing date to avoid multiple cycles of billing, which we currently do. This will cut down administrative costs. It will also give sponsors more sense in predictability in their annual fee burden.

We're adding a limitation to no more than five program fees for products identified in each application. So not to disincentivize additional dosages of that form or strengths.

And a little known waiver that is little used proposing discontinue to enhance our administration of the program and to improve our data collection efforts is discontinuing the fees-exceed-the-cost waiver.

To continue a little bit more diving into the fee adjustments, really focusing on two areas here. For those of you familiar with workload adjuster, that gives us the ability to adjust fees year to year based on workload. It's actually -- I'll

go on record saying it's a bit of a rudimentary tool at the moment and was put in place when that was what existed. We're looking to make some short-term enhancements to that, such as including meetings in the workload adjuster as a proxy of workload.

But the ultimate goal is to replace this, and it's going to be replaced with a capacity adjustment, which I talked about in the first capacity planning methodology that will be assessed once it's up and running by an independent party to look at the methodology to see if it's reasonable and accurate, and that will be published for public comment.

Once that's published, we'll have the ability to use the capacity adjustment.

And the proposal, replace the 5-year offset and the final year adjustment with an annual operating reserve. Not really a new concept, a combination of the two.

The 5-year offset, if you're familiar, if folks have looked at the fees in FY17 FR Notice, you'll see there is a reduction in fees in FY17. It's because we're offsetting excess collections for 4

years estimated last year. We're offsetting $124 million. And there is also an opportunity to take a final year adjustment, which has happened in the past, in case there is not a reauthorization, you can have a timely winding down of the staff, laying them off, if such a catastrophic thing were to happen. That has never happened, of course, thanks to everyone in this room. So we saw no need to continue to do that.

So these two requirements, statutory requirements, the 5-year offset final year adjustment did place some restrictions on our financial management where you have to plan multiple years out, how much are we going to have to offset? What is that estimation going to be? And then that limits your hiring, that limits your planning.

We saw replacing this with something that is more agile and flexible year to year, an operating reserve adjustment as a prudent step to giving us carryover balances of a certain amount that would allow us to weather storms in collections, if that happens, but also not collecting too much. So there would be an offsetting of fees the next fiscal year if

we do exceed a certain amount.

I will say the dollar figures that are in the FR Notice, there was a lot of analysis that went into that. That amount is precisely calculated to fund only what's in this agreement and nothing more, and that's our staffing amounts.

Thank you.

MS. VAIDYA: Thank you, Andy, Theresa, and Brad.

So I think we all know the drill. Now we'll turn it over to our panel of stakeholders so that they can provide their views on the recommendations. And I'll start off with Janet.

MS. MARCHIBRODA: Thank you for the opportunity to share our comments on the proposed commitment letter for PDUFA VI. I'm with the Bipartisan Policy Center. We're a nonprofit organization that was formed by former Senate majority leaders on both sides of the aisle, and we try to find common ground on a whole range of issues: economic policy, energy, immigration, and, of course, health care.

So I run the health innovation effort. And actually, back in July of 2015, under the guidance of former Senate Majority Leader Bill Frist, a Republican, and Representative Bart Gordon, a Democrat, and a wonderful group of Advisory Committee members, we actually came up with a list of 19 recommendations that we would love to see advance in policy, and we were delighted to see that 7 of the 19 are actually in the proposed commitment letter.

And I know I'm not supposed to talk about all of those, but we were really excited to see the provisions on real-world evidence, the patient input, the combination products. But we'll pull together our formal letter.

But, you know, I'll tell you, in all the conversations, one of the most important areas, which really is the foundation for everything, all the goals that we care about in accelerating the development and delivery of safe and effective treatments and cures to patients is really about the capacity of the FDA. And we were so excited and delighted to see all of the HR-related provisions in the letter.

I won't, in the interest of time -- you know, the corporate recruiting, the efficiencies that Theresa talked about, the use of contracted resources to help augment the hiring that needs to be done, the focus on scientific-focused recruiting, and the compensation analysis in particular was important.

And it's been illuminated previously, but it's tough. It's hard for FDA to keep up, and we're really glad to see the analysis of compensation. We would love to see more, but know that not all of that can be accomplished here, things like direct hires and increasing the number of employees that can exceed the cap. But in any event, we're really happy to see these measures to improve the HR infrastructure.

The other thing -- and this was actually a specific recommendation that we had -- this comprehensive and ongoing assessment we thought was really important to have somebody come in and sort of help figure out root cause analysis to support FDA and improving its hiring process. And then, finally, I'm going to stop there.

We were also pleased, of course, we do a lot

of work in technology to see a number of the recommendations associated with electronic submission processes. And I won't actually comment on the third area.

So, again, offer our formal comments next week, and we appreciate the opportunity to share our insights today. Thank you.

MS. VAIDYA: Thank you, Janet.

Next, Cynthia.

MS. BENS: Thanks, everybody. And for those of you who weren't here this morning, I'm just going to do a quick overview. I'm Cynthia Bens. I serve as Vice President of Public Policy at the Alliance for Aging Research. And I also serve as Executive Director of two coalitions that's focused on FDA regulatory issues. One is called Accelerate Cures and Treatments for Alzheimer's Disease and the other is Aging in Motion, which is focused on physical frailty in the elderly.

I'm going to spend the next few minutes talking about what we think is really the most critical part of the PDUFA VI commitment letter, and

it's Section 3, and get ready because there are a lot of glassy eyes in the audience, and so I know it's not super sexy to everybody, but it's come up quite a few times today that staff capacity is really something that's important.

So we think that all of the recommendations under Section 3 that have to do with improvements to FDA's hiring and staff retention are really the most critical in making sure that all of the things that we all love about PDUFA VI happen.

One of the things that came up in Dr. Woodcock's introduction this morning is that FDA needs the best and brightest people in the right positions, and there needs to be continued stability in the workforce. And we know that FDA really does need to compete with both the private sector, but also one of the things that doesn't get mentioned much is that they're competing with other federal agencies for many of the same people, so a number of the changes under Section 3 are very important to us.

We recognize that FDA lacks a number of the tools it needs to play on that level playing field, so

we really push for -- I'm not going to take credit for all the recommendations of the commitment letter, but we really push for hiring to be a part of this agreement and also part of H.R. 6, the 21st Century Cures Act, and the Senate Innovation Bill.

We're really pleased to see that FDA put industry user fees to support all the necessary changes that FDA needs to make. And there are a few sections that I'm going to call attention to, but I promise to stay within my 3 minutes.

The first is Section 3A, the modernization of FDA's hiring system. The two highlights I would like to bring up in this section are FDA's commitment to reviewing a cataloging of the existing position announcements in order to implement a comprehensive online position classification system, and this gets at one of the points Theresa made earlier about the number of position announcements that are out there.

But the effective transition of that position announcement that's time-limited to a common vacancy announcement, that's not time-limited, that's available on more of a rolling basis, this is really

going to help us shift for a number of the review divisions within the Human Drug Review Program looking at specific scientific and technological needs within the review division, and it's going to give people access to apply for these types of positions outside of there being an open position announcement. So we think those are really two very positive steps forward.

The second noteworthy section is Section 3B, the augmentation of hiring capacity, and this has been brought up a couple of times. But not only is FDA going to be able to supplement their in-house staff with external expertise, but by bringing in these qualified hiring contractors, this whole assessment process is going to take place, and we think that that's really important when there are new things like the Breakthrough pathway program that's been wildly successful and knowing what it's going to take to actually put these programs into practice.

And it seems, when you first read the commitment letter that it's only going to be FDA and industry that's assessing this on an ongoing basis,

but I would like to highlight something Theresa brought up earlier, that there is going to be no less than three public meetings. So I think it's really beneficial for groups like ours and some of the folks that spoke on Panel 2 who really care about regulatory tools and making sure FDA has the expertise to participate in these public meetings as they happen, to talk about how we think that those needs are going to be met.

And then the third section I would like to mention is establishing a dedicated unit within the Office of Medical Products and Tobacco with continuous focus on hiring staffing. I think that one of the comments that I heard earlier is that FDA fears letting some people out of the office because they might get poached by industry.

FDA should have the same ability to poach back, and we think that by having this office that's really focused on proactively reaching out and looking for where the scientific and technological advances are going and where the resource needs are, that it's going to help FDA greatly.

And then, last but not least, Section 3D, that's dealing with FDA setting hiring goals within PDUFA VI, this section really demonstrates to us the commitment that the Agency has to accountability and also making sure that they're being very targeted in their focus of where the hires are going to happen to strengthen the review process, so we think that they should be applauded for that, taking that step.

And so I'm going to stop there and thank you all for your attention, but our organization fully supports Section 3 and would like to be able to be a resource to FDA as they get all the people they need to make this package happen.

MS. VAIDYA: Thank you, Cynthia.

Jeff.

DR. ALLEN: Thanks. So I think I can be brief, too. Obviously this is an important provision and at the cornerstone of making sure that any of this can work in terms of having the ability to recruit new employees to the FDA.

So I think while a lot of obviously today's discussion has been focused around enhancements to the

PDUFA program, this has elements that I think could help us as third-party stakeholders advocate for other areas beyond just the PDUFA agreement by having this level of accountability.

Those of us who have spent a fair amount of time involved with advocating for additional resources for FDA -- Cynthia and I both have had the opportunity to lead the Alliance for a Stronger FDA -- we're always asked from the Hill, "We hear you, you want more resources for this agency, but we need specifics in order to justify it," and having this level of accountability and capacity planning will help us make that case as well. And I know that's outside the scope of this agreement letter, but I think it is an opportunity that could come of this.

And also I think it's important as we're talking about the strains on such a critical agency here that we also recognize and keep focused on where things are. This is the gold standard agency. Eighty percent or so of its resources go to its people, and these are individuals that are subject to all of the growing responsibilities that are continuously added

to them without always having the resources to accompany that, and they do so because they believe in most cases that it's the right thing to do.

And we've had the good fortune of working with a number of those experts and their willingness to provide time to scientific projects, some good ideas, probably some less good, but they're willing to work with us in trying to look at what some of those opportunities are, and it has nothing to do with the PDUFA framework, it's just an added kind of stress to the system here.

But being able to account for that and the importance of it will allow it to continue and hopefully we can advocate for that side of the FDA budget in addition to what's contained in the user fee program here.

While I'm off topic, I'll stay off topic and just say that as this moves forward into the congressional space, one thing that isn't possible to address in the agreement letter but could be an opportunity from potential legislative vehicles are things related to the retention side of things and

looking at ways to make a career at FDA more equitable compared to other sectors. And this could be achieved through legislation and looking at things like raising caps for eligibility to enhance salary programs and the amounts associated with these programs could be an opportunity moving forward as well.

MS. VAIDYA: Thank you, Jeff.

Sascha?

DR. HAVEFIELD: Thank you. And, folks, I think I may be repeating everything you just said, but you may have heard already today that the hiring provisions are critically important to us. So all joking aside, a stable and sustainable workforce is crucial to the FDA's ability to fulfill its public health mission and keeping pace with scientific advances and drug development over the years, and this was especially true in PDUFA V.

FDA has faced significant human resource challenges that have negatively affected the Agency's Human Drug Review Program and the advancement of regulatory sciences. So PDUFA VI seeks to remedy this by helping to ensure that the FDA is adequately

resourced and staffed to support a regulatory review and approval process for new medicines that are scientifically sound, efficient, and predictable.

On electronic submissions and data standards, I think Brad gave an in-depth review, and there is very little to add here.

Hiring we just covered.

So from an enhancing management of PDUFA resources and financial predictability, stability, and efficiency, again, it goes hand-in-hand with the hiring provisions. But PDUFA VI supports common-sense financial reforms, as we call them, that provide greater predictability for the Agency and sponsors. These reforms include reducing FDA's administrative burden, which is important, and operating expenses for the PDUFA program.

FDA will further implement a full-time reporting system, as you heard from Andrew Kish, and establish a professional capacity planning function to better attract workload, identify areas of need, and help reallocate resources when necessary, all that to ensure that the program remains adequately and

appropriately funded in the future.

So in closing, since this is also the last panel, so I'm going to go off topic now, so in closing, PDUFA is, in my mind, a shining example of a program that has produced positive and tangible results that matter not only to patients, but they drive innovation.

PDUFA VI will help ensure that FDA's review process for new medicines keeps pace with biopharmaceutical innovation and 21st century regulatory sciences while delivering safe and effective innovative treatments and cures to patients. And so PDUFA VI will play a critical role as we continue working together to help patients live longer and healthier lives.

So with the conclusion of the PDUFA VI technical negotiations phase, PhRMA looks forward to working with Congress, the administration, patient and medical provider groups, the FDA, and all stakeholders that are here in the room to ensure timely reauthorization of this very, very important program.

So thank you again for the opportunity to

participate in the public meeting on behalf of PhRMA. And back to you.

MS. VAIDYA: Thank you, Sascha.

And, Kay.

MS. HOLCOMBE: I just want to make three points, which I will be able to make 10 minutes each.

First of all, with respect to IT, I think everyone who has a computer -- and isn't that everyone? -- realizes that there are some incredible frustrations. And if you can imagine, even a more incredible frustration than having that little spinning thing while you're trying to like log on to something like, shall I say, ebay.com, if you are having that little spinning thing while you are trying to upload your application, which you promised the CEO of your company was going to be at the FDA by tomorrow morning, and you get that little spinning thing and you can't upload, that is the ultimate frustration.

And I really think that what Brad and our technical negotiators have accomplished here with these commitments is going to make this whole system of electronically submitting applications and FDA

receiving them in a form that they are usable by all of the reviewers is going to happen, and it's going to be a tremendous advance.

With respect to hiring, everything that could be said probably has been said, but I want to emphasize what other people have said, which is that the support for FDA having on board the people it needs to do the task has to come from the top of the Agency and the top of the department down.

The FDA commissioner needs to be involved in aggressively supporting the needs of the centers in terms of their hiring. And I believe that having these hiring goals built into PDUFA is going to place that attention on that necessity so that it will have the attention of the top of the Agency and the top of the department.

I think that everyone needs to realize that having a shortfall in the Office of New Drugs of 200 or more people is not just an OND problem, it's not just a CDER or a CBER problem, this is a public health problem, and we need to solve this problem, and this PDUFA agreement attempts to do that by enhancing, as

Theresa described, the activities related to recruitment and bringing on board qualified experts in all of the various disciplines that FDA needs to do its job.

With respect to financial, I want to thank Andy Kish for not treating me in particular like a dummy because I didn't completely understand what he was talking about all the time, but he sure persuaded me by the end of this that the way things were happening before needed to change, and they were going to change to my advantage because what I came in saying was PDUFA needs to be financially viable over the long term, and what FDA convinced me of is that PDUFA will be financially viable over the long term with the changes that are made here.

And I want to point out in particular capacity planning. There isn't a company in the biopharmaceutical industry that does not do capacity planning, because capacity planning is what allows you to know how you can take a project forward over the next 5 years. If you need a hundred more people to do something, and you have to hire a hundred people

within the next 2 weeks, you are not going to do that project.

And capacity planning is going to allow FDA to make the kinds of business-smart decisions that biopharm companies make every day. If we need five people, that's doable, so let's figure out how to know -- and we will know that through continuous time reporting -- how many people do we need? How many FTEs can dance on the head of a pin? And we need to lay that out in advance so that we can achieve that in advance.

I think the other thing -- and this sort of goes through the entire PDUFA VI agreement -- through all of these things -- the financial planning, the IT, hiring -- we have transparency, we have public involvement, we have the use of outside experts, we have the use of outside evaluators, and this is a thread that runs through this entire PDUFA VI agreement.

FDA is saying to us, "We don't think we can do this on our own. We need to work as a team to achieve all of these things." The Agency, the

regulated industry, patient organizations, caregivers, other stakeholders, we all need to participate, as Cynthia already said, in these meetings, in these opportunities that we all will have, to work with FDA to make this PDUFA agreement, which we believe can be a game-changer for drug development, to make it happen the way we want it to happen. We will not have early warning that things are maybe going off the rails unless we participate.

So my bottom line is BIO strongly supports this agreement and looks forward to working with FDA to implement all of these provisions, and we look forward to working with all of the stakeholders and Congress as Congress moves this legislation to have this program reauthorized in a timely way.

And I want to thank again FDA for allowing BIO to participate in this meeting.

MS. VAIDYA: Thank you, Kay.

And I would like to thank all of our panelists today.

Open Public Comment

MS. VAIDYA: So now we're going to move into

the Open Public Comment session.

And before that, I would like to ask our FDA subgroup negotiation leads to please come up to the front during this time.

Okay. So now we are moving into the Open Public Comment session. Your comments that are presented today will be transcribed and be part of the public record as well as the rest of the meeting today. Since we would like this to be a transparent process, we encourage you to note any financial interests that you have that are related to your comments. And if you do not have such interests, please also state that for the record as well.

So we have collected sign-up before the meeting and during the break. We have seven people signed up. So please be respectful for your other colleagues here and stick to the 5-minute time limit. I'll be keeping track of time. Once you approach the 4-minute mark, I will try to ask you to start wrapping up, and give you a hard fast stop at 5 minutes.

And before that, I'll run through the names that we have, I have, listed here. I know this is out

there, so some people thought this might be a registration sheet, so I just want to confirm these names.

So we have Peter Pitts, Sharon Terry. Adrian Hernandez? Okay. Seronjit Garcha? No. Okay. Penny Levin, Karin Bolte, and then Paul Brown. Okay. Great.

So first can we start off with Peter Pitts?

MR. PITTS: Good afternoon. My name is Peter Pitts. I'm the President of the Center for Medicine and the Public Interest. I'm a former FDA associate commissioner, and I am here on my own dime.

Once considered junk science, real-world evidence is the new star on the precision medicine horizon, but the tool set for using this treasure trove of health care information is nascent, and the tasks are as daunting as the opportunities. The good news is that the FDA is taking this challenge to heart and per the PDUFA VI commitment letter in writing.

A key insight to consider comes from J.M. Eisenberg's advice: globalize the evidence, localize the decision.

As with everything to do with the advancement of regulatory science, much depends on the willingness and ability to implement change based on infrastructure, capabilities, and trust. The end goal is the same for all stakeholders, ensuring optimal use of resources for health care systems, improving access to value-added medicines for patients, and appropriate reward for innovation.

To evaluate the reliability of data, FDA must assess how they were collected, their adequacy for answering relevant questions, and whether they were collected in a manner that minimizes bias.

This brings into focus a key point: big data and valid evidence are not the same thing. There is an important distinction that illuminates a crucial difference. When it comes to the patient voice, or any voice, the plural of anecdote isn't data, but the plural of data is science.

Patient passion is important to share. When combined with data and a more dispassionate understanding of regulatory paradigms, a patient-driven pathway can and must evolve into a tool used to

impact regulatory decision-making.

Terry Toigo quoted from a blog by Rob Califf and Rachel Sherman. Let me add to that. Both Califf and Sherman say: We need to develop proposals that modernize the information used in the evaluation of the value of treatments. Just as the key scientific insights got in the FDA Critical Path Program are genetic variations and biomedical informatics that predict and inform individual responses to treatment, we must establish a science-based process and incorporate the knowledge and tools of personalized medicine in reimbursement decisions, true evidence-based patient-centric medicine.

We need a critical path for real-world evidence to continue the process of developing the tools, such as electronic health records, that can be used to improve the predictive and prospective nature of clinical outcomes.

In an era of personalized medicine, one-size-fits-all treatments and reimbursement strategies are dangerously outdated. Accepting real-world evidence does not mean discarding the randomized gold

standard, it means augmenting it.

When it comes to the regulatory science of real world evidence, as Theresa Mullins said early in the day, the devil is in the details, but perhaps a more appropriate way to think about is a quote from Admiral Rickover, who said, The devil is in the details, but so is salvation.

Thank you.

MS. VAIDYA: Thank you, Peter.

Next we'll have Sharon Terry, please.

MS. TERRY: Thanks very much for this opportunity. I have no financial conflict of interest.

I am Sharon Terry, President and CEO of Genetic Alliance, a organization with a 30-year history of empowering individuals, families, and communities to take charge of their health.

Genetic Alliance is a large network of 10,000 disease advocacy and community organizations, sharing information and resources, developing novel tools, and empowering people to drive research.

I also serve as the co-principal

investigator of PCORnet, the National Patient-Centered Clinical Research Network, chair of its Engagement Committee, and PI of one of the Patient-Powered Research Networks.

PCORnet is an innovative initiative of the Patient-Centered Outcomes Research Institute designed to conduct clinical research faster, easier, and less costly than traditional methods by recognizing that research must be driven by the power of people and their communities.

PCORnet is changing the culture of clinical research from one solely directed by researchers to one driven by the needs of patients and those who care for them. We stand in strong support of the PDUFA VI commitment letter.

Both Genetic Alliance and PCORnet know the value of meaningfully engaging participants as partners in research and authentically engaging communities. We know that the required revolution of the drug development enterprise requires a consumer-driven movement. It is people, the patients, the families, who are core to this movement.

Every moment, there are patient experiences occurring, but they are not being included in a formal way for evidence. Patients expect that we continue to learn from their experiences to improve the experience of those who walk in their shoes the next time. Unfortunately, that doesn't happen today. PDUFA VI would promote that approach through the emphasis of real-world evidence. My colleague, Adrian Hernandez, of Duke and PCORnet, will address that more completely after me.

As such, with dedication to improve health outcomes for all Americans, it is critical that we continue to facilitate and encourage patients at the center of the development and regulatory review process.

With PDUFA VI, we have the opportunity to build on FDA's ability to improve and advance drug development and regulation, accelerate the development and availability of new medications for people in need, encourage innovation, and ensure that the FDA can recruit and retain the expertise needed to carry out these goals.

This reauthorization builds on the successes of the previous PDUFA agreements to ensure patient safety and promote timely access to safe, effective, and innovative medicines. It is critical that we continue to adopt interventions based on community involvement, patient-reported outcomes, and the preferences of those who know best, the patients who will use these medications and products.

Over the last several of years, Genetic Alliance has used our platform for engaging everyone responsibly to solicit input from individuals affected by sickle cell, inflammatory bowel disease, and idiopathic pulmonary fibrosis to enhance the patient-focused drug development efforts.

Working with relevant advocacy organizations, we were able to capture hundreds of individuals' concerns, experiences, and questions about their conditions. This information was analyzed and presented to the FDA, recognizing that patient perspectives are critical to improving drug development.

We are excited to see PDUFA VI advancing the

use of structured benefit-risk considerations to help inform and guide regulatory decision-making.

Throughout the process of engaging these communities, we interacted with competent and dedicated FDA staff, as I have for over the past 20 years. We know that a strong scientific and medical force is essential to carrying out the public health mission, and are pleased to see that PDUFA VI will enhance the FDA's hiring and workforce management strategy. This is essential to the nation's health.

Further, as the parent of two adult children with a rare genetic condition, and the founder of the advocacy group representing that condition, I am encouraged by PDUFA's continued ability to advance the development and approval of medicines for rare diseases, including rare pediatric diseases.

We fully support the PDUFA VI and appreciate this opportunity to comment. We look forward to partnering with diverse stakeholders to empower people to accelerate the change we all seek.

Thank you.

MS. VAIDYA: Thank you, Sharon.

Next can I have Adrian Hernandez?

DR. HERNANDEZ: Hello. So I want to thank you for allowing us to have this public comment period. I am Adrian Hernandez, a cardiologist at Duke University and Director of Health Services and Outcomes Research at the Duke Clinical Research Institute. I have had relationships with industry funding research at Duke, and those are online and available for anyone to view.

As Sharon noted, I am also the coordinating center PI for PCORnet, the National Patient-Centered Outcomes Research Network, and many of the topics that have been brought up today regarding PDUFA VI is quite important for our nation's research capacity.

Like many of the people in this room, I am also a father, a brother, and son of family members who have conditions that would actually be improved with better evidence, especially evidence from real-world evidence development and also, importantly, for engagement of the patient voice in terms of understanding what's the right therapies and what are the right outcomes that would be important for those

conditions.

So through these lens, across these different perspectives, I am here today to support FDA's commitment towards real-world evidence generation and incorporating the patient voice into regulatory decision-making.

So, for example, since the founding of DCRI, clinicians and researchers have come together (inaudible) through clinical trials and observational studies. Often these observational studies are outcomes research studies of real life experiences of patients who routinely walk through our health systems nationwide.

In our ideal state, we actually generate evidence from both worlds together; that is, we generate evidence from clinical trials integrated with the real world, or what's often termed pragmatic clinical trials.

In part, the rationale for this approach is too often our clinical trials represent a highly selected or small subset of patients that we treat every day. This leaves us with questions as well as

our patients regarding both the safety and effectiveness of medical products used in everyday practice.

In addition, as Sharon noted, our patients expect that we have learned from the experience of others who have been treated in that past. Logically, as medical products are on the market, we should have greater and greater understanding of the risks and benefits beyond what was generated from the original clinical trials, especially in areas where therapies are being extended beyond what their original labeled indication was.

So from the learnings today, an example of that is evidence generated from Sentinel that has shown what's possible in understanding the safety of medical products, as used in the real world. In a similar fashion, we have generated evidence from clinical registries that has provided information regarding the right treatment for the right patient at the right time across different areas, such as acute coronary syndrome, heart (inaudible) and stroke care. However, how that information gets to patients or

clinicians in a standard, trustworthy manner, such as part of the medical product label, is not clear.

Regarding PCORnet, over the years many people have noted our current research system is too slow, too costly, and often is short in answering the questions that matter the most to people. So the creation of PCORnet has really been intended to address those flaws.

PCORnet aims to unite patients, clinicians, and health systems together as the national system to support a learning U.S. health care system to enable large-scale clinical research conducted with enhanced quality and efficiency.

Our mission is truly to enable faster, more trustworthy clinical research that helps people make informed health decisions. And when we say "people," we mean all people, so clinicians, patients, health system leaders, regulators, and payers, and others participating in the health care system.

This system relies not only on a foundation of electronic medical records mapped to accommodate them all, but also incorporating that patients are

participants' voice throughout all of our studies.

To date, PCORnet includes data from approximately 140 million people across the U.S. who are aiming to do both large observational studies as well as pragmatic randomized clinical trials with high quality that matter to all people. While having a framework that guides how real-world evidence from such a system as PCORnet may be useful, the FDA can really realize a massive opportunity to improve (inaudible) space.

We can hopefully reduce the mass of redundancy that exists by having parallel universes of health care delivery versus our clinical research system, and we can incorporate real-world data from our health care encounters for patient-reported outcomes and other data generated in the real world. This will allow us to have a more efficient process to generate answers to many more questions faced by multiple stakeholders.

So in summary, we strongly support PDUFA VI reauthorization. We know no evidence leaves us with too many questions, a little evidence may be helpful,

but a lot of evidence, especially from the real world, can go a long way towards improving the health of people every day.

Thanks again for allowing us to comment, and we look forward to the further progress for PDUFA VI.

MS. VAIDYA: Thank you, Adrian.

Next we have Penny Levin.

MS. LEVIN: Hi. My name is Penny Levin, and I'm here on behalf of -- I represent Global Regulatory Intelligence and Policy at Teva Pharmaceuticals. And I have no financial interests.

First, I really want to thank FDA and the representatives from BIO and PhRMA because I just wholeheartedly support, and my company, PDUFA VI. I've been in the industry since the initiation of PDUFA, and I've watched the advances. I started in clinical myself and have always been close to the patients, so I can't say enough how much and how smooth the negotiations went and how everyone was really heard.

So I first want to thank everyone for that. I know how much work goes into it and I know how hard

it is, so I'm most appreciative.

So my speech. Teva is a leading global pharmaceutical company. We are committed to increasing access to high quality health care by developing, producing, and marketing affordable generic drugs and innovative specialty pharmaceuticals and active pharmaceutical ingredients.

Teva supports a balanced regulatory policy rooted in science so that it appropriately incentivizes innovation while also facilitates the development and time approval of affordable generic medicines for the American public.

Today, one in three of Americans use a Teva prescription medicine. We directly employ more than 6,500 Americans and support another 40,000 in direct U.S. jobs with an economic value added of around $9.2 billion in the U.S. last year.

Globally, Teva has present in 60 countries around the world in sales in 100 markets serving more than 20 million lives every day and enabling more and more nations to meet health care needs and to improve patient access to medicines. I say that again because

of our commitment to patients.

At one point, I worked on the products myself and brought nine drugs to market, but moving into a policy role, I was really able to see the patient lives and how important policy is in making that access.

Teva supports the PDUFA VI proposal recently completed. We believe some of the key accomplishments -- and I don't want to be redundant, but I think everyone really hit the nail on the nuttle (ph) with the points, but a few key points that we want to emphasize. We feel accomplishments that will occur with PDUFA VI include the significant strengthening of efforts to incorporate the patient perspective into development and regulatory review process for innovative medicines. This will likely translate to increased innovation of medicines for unmet medical needs and truly get to what is important to the patient.

Second, expanding upon advances in medical innovation in 21st regulatory science. Three examples, of course, include the use of real-world

evidence for regulatory decision-making. Teva supports using real-world evidence to better understand how patients use their medicine, and ultimately with guidance, we can develop prospective protocols with predefined RWE endpoints both in product development as well as to help in fulfilling post-approval understanding of the products.

Facilitating use of innovative clinical trial approaches in efforts to translate to greater efficiency of the drug development process, Teva supports these ongoing efforts to advance clinical trial efficiency to help bring innovative medicines to our American patients in a most expedited manner while ensuring the medicines are evaluated comprehensively and with most current science.

Lastly, to establish a dedicated process to improve the biomarker qualification pathway to enhance the development and ability to use surrogate endpoints in drug development. Such efforts are critical for us to develop medicines for unmet needs. We support the ongoing efforts to advance the biomarker qualification process to keep up with the advances in the science.

Such efforts can truly help us to ascribe the real value, both patient benefits and enhanced safe use, of these medicines for our American patients.

Lastly, I would like to discuss reforms to the financial model that we believe will provide greater transparency and predictability for FDA's Human Drug Review Program.

Teva supports the proposed changes and believes they will help encourage ongoing industry innovation to learn more and more about their medicines beyond the initial approvals, providing supplements to the Agency in efforts to enhance their labels, providing prescribers and patients with the most current safety and efficacy information.

It will also shift many of the fees to when products are closer to revenue in their life cycle, therefore, helping companies working on orphan products or developing medicines for unmet needs and bringing such medicines more efficiently to the American public.

In summary, Teva believes the enhancements and changes proposed in PDUFA VI will result in more

efficient drug development and review and will continue to translate to an increase in first-time approvals, bringing innovative medicines to the American public.

Thank you.

MS. VAIDYA: Thank you, Penny.

Next we have Karin Bolte.

MS. BOLTE: Hi. It's Karin Bolte.

I'm Karin Bolte. I'm the Health Policy Director with the National Consumers League. Founded in 1899, the National Consumers League is the nation's oldest consumer advocacy organization. We receive our funding from a wide variety of sources, including nonprofit organizations, associations, corporate support, including from the pharmaceutical industry, foundation grants, and government grants, including the FDA.

We will submit more complete written comments, but this is just a summary.

PDUFA VI lays out an ambitious and admirable agenda for increased FDA attention and focus demonstrating how the expansion of FDA's drug approval

work is made possible by the PDUFA User Fee Program.

That said, as PDUFA VI moves through the reauthorization process, NCL urges the FDA to remain mindful of the concerns expressed by some that because industry pays user fees, industry thereby controls the FDA's agenda and process. It is critical for the Agency to act independently of industry influence and to uphold its high standards for safety, efficacy, and quality of prescription drugs.

While it is important to have an efficient and timely approval process, NCL believes that there is still too little emphasis in PDUFA VI on performance goals and at improving the safety and efficacy of drugs. We note that PDUFA VI does not call for an assessment of how well the Agency's data systems and processes support the review, oversight, and communication of post-marketing safety issues until the end of fiscal year 2022. We urge the Agency to speed up the timeline for this important assessment.

While NCL believes that drug makers should receive a fair return on their research and

development investment, we also believe that drugs should be fairly priced. To improve competition, FDA should prioritize the review of those drug and biologic products for which no competition exists in the marketplace. And, although while not the subject of this proceeding, we also believe that NCL should be provided with the necessary resources to address the current backlog of nearly 4,000 generic drug applications.

In addition, we believe that FDA should examine its rare disease program to ensure that it is not being misused, especially in the case of older drugs that are being reclassified as orphan drugs.

In reviewing the proposed PDUFA VI agreement, NCL notes that it has many good features, including the following. NCL supports PDUFA VI emphasis on improving communication between FDA and product sponsors.

We support the provisions in PDUFA VI that will enhance incorporation of the patient and caregiver perspective in drug development and decision-making. Along these lines, we want to

suggest that perhaps FDA create a fund for patients wishing to attend and speak at an FDA workshop but who cannot afford the expense involved to get to Washington.

NCL also supports the provision of additional resources for the Breakthrough Therapy program. We applaud the PDUFA VI further investment of $50 million in the Sentinel System and believe that it is critically important for independent researchers to have access to Sentinel and similar surveillance databases such as the IMEDS program.

As pretty much everyone has previously stated, we believe that enhancing FDA's ability to hire and retain a highly qualified drug review staff is one of the most important components of PDUFA VI.

NCL urges FDA to include consumer organizations in stakeholder meetings and discussions. The consumer viewpoint is separate and distinct from the patient voice, and both need to be heard.

NCL also has some recommendations for additional PDUFA VI activities. NCL believes that a portion of PDUFA funding should be directed towards

examining the safety of off-label prescribing to address consumers' lack of awareness and understanding of the practice. We also believe that it is imperative for the FDA to have the staff and resources to ensure that direct-to-consumer drug 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 so that misleading information does not reach consumers.

We believe that user fees should be allocated to support the hiring of additional staff to review DTC ads.

In closing, NCL applauds the FDA for growing PDUFA since its inception in 1992 to a far more robust, efficient, and effective program that strives to deliver the world's most safe, effective, and high quality drugs.

Thank you for the opportunity to share our views with you today.

MS. VAIDYA: Thank you, Karin.

And, lastly, we have Paul Brown.

MR. BROWN: Good afternoon. Can you hear me okay? I can't tell if it's on speaker.

Before I start, I'm Paul Brown, with the National Center for Health Research. I'm Government Relations Manager. Our Center is a think-tank. We focus on health care for adults and children. We do not have any conflicts of interest. We do not receive money from drug makers, device makers, insurance companies, anything like that.

I want to echo that our Center supports NCL's comments. I thought they were very good and right on the mark.

We respect the FDA, and we're committed to ensuring that it has the resources it needs to keep our medical products safe. Given the inadequate appropriations provided to the FDA, we strongly support increasing user fees to improve FDA's resources.

Just as an aside, if I had to summary today's panels and whatever everybody else has said, everyone is really supportive of the commitment letter. It's almost like puppy dogs and rainbows.

However, with rainbows, you do get clouds, and I'm going to mention a few clouds.

Our Center is disappointed that the focus of the FDA commitment letter is on speed. The commitment letter states that PDUFA's intent is to provide additional revenues so the FDA can make medicines available to patients sooner without compromising quality or FDA's high standards for safety and efficacy.

However, in the 46-page PDUFA VI commitment letter, only about 2 pages are devoted to FDA's safety system. User fees should focus more on improving the safety and efficacy of drugs, not just the speed of approval.

In PDUFA V, our Center supported earlier and increased meetings between FDA and drug companies. PDUFA VI, as you know, calls for even more meetings. The result is that the percentage of drugs that the FDA is approving is higher than ever. But that isn't necessarily a good result because recent studies have shown that too many of these drugs are not effective, and I'll get back to that in a minute.

FDA's primary mission is protecting the public health by assuring safety and efficacy of medical products. User fees should fund an independent review of how the program has affected the overall public health. Have user fees changed FDA's priorities? Is FDA now treating industry as a customer that it needs to please instead of acting as a regulator to ensure the public health?

Regarding Sentinel, we agree it deserves additional funding. However, we urge the FDA to make a Sentinel database available to independent researchers, the same as NCL did, so they can form their own assessments of drug safety. This is essential because FDA is approving more and more drugs through expedited approval pathways based on surrogate endpoints and other preliminary evidence.

In addition, the smaller, shorter studies, typical of expedited pathways, provide inadequate evidence of safety, since uncommon and long-term risk are unlikely to be evident.

I'm going to touch a minute on drug costs. I know that's not the focus of FDA. Although FDA does

not directly influence the price of drugs, they are indirectly contributing to skyrocketing costs of drugs by approving products that have little, if any, benefit. For example, a thyroid cancer drug that the FDA approved on preliminary data is no better than placebo for thyroid cancer, and yet our Center has learned that it costs $169,000 per year per patient. That's way too much, and we need to address that issue. Maybe we can use user fees to address the efficacy on that.

PDUFA VI also emphasizes a flexible approach to approving drugs based on biomarkers and other research designs that may show promising results that are ultimately found to be nothing but false hope. These faster, less thorough reviews, will cost patients and taxpayers billions of dollars, but many will later be found to offer risks that far outweigh the benefits. When happens, the FDA needs to have access to user fee funds to rescind approval quickly.

I'm going to touch briefly on off-label. PDUFA VI should provide funding to monitor off-label use of drugs. Although physicians may use their own

judgment to prescribe drugs off-label, drugs used in this manner have less information about the benefits and harms. A JAMA internal medicine article stated that researchers found a 54 percent increase in adverse events when drugs were prescribed off-label. With PDUFA funding, FDA could identify the top drugs prescribed off-label and target them for increased post-market surveillance.

PDUFA funds should also be used to help monitor direct-to-consumer ads. In 2015, PhRMA spent $5.4 billion on direct-to-consumer ads. There is a need to carefully review all the ads to reduce the misuse of prescription drugs, such as atypical antipsychotic drugs advertised as if they were antidepressants. PDUFA fees should be used to enhance DDMAC, Division of Drug Marketing, Advertising, and Communications.

In conclusion, the FDA has been underfunded for years, and user fees are necessary. FDA is struggling to manage expanded demand with inadequate appropriations. While we are happy about the increased resources for Sentinel and for hiring and

retaining employees, we are not convinced that the increased PDUFA fees will adequately cover the increased workload, especially because they're such intensive workloads, such as meetings, drafting guidance documents, public workshops, and, of course, the industry face-to-face -- I think they mentioned earlier today 3,000 meetings, and only 2 or 3 percent of them were rejected.

One final thing, I was glad to be here, glad to have the opportunity to speak. I was very disappointed that there were no consumer groups on the panels. It seemed like you used the same folks on multiple panels. I know our organization was not contacted to be on a panel. I know that National Consumers League was not. I hope that some of the other groups, such as Consumers Union, Public Citizen, US PIRG, can be involved in these discussions. I think they'll add a different point of view and a useful point of view.

Thank you.

MS. VAIDYA: Thank you, Paul.

And that concludes our open public comment

session. I would like to thank you all for coming here today and sharing your views on the recommendations for the reauthorization of PDUFA.

As a reminder, I just want to let you know that our public docket will remain open until next Monday, which is August 22nd. So it has been open for about 3 weeks now, so this is the final week. So please send in any additional comments that you may have. With that, I will let you all go. Thank you so much.

(Whereupon, at 1:48 p.m., the meeting was adjourned.)

CERTIFICATE OF NOTARY PUBLIC

I, MICHAEL FARKAS, 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.

MICHAEL FARKAS
Notary Public in and for the
State of Maryland

My commission expires: 06/27/2018
Notary Registration No.: 256324

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I, DEBORAH J. ARBOGAST, 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.

August 25, 2016 Deborah J. Arbogast