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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
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

Reported by: Michael Farkas
Capital Reporting Company

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- Jeff Allen, Friends of Cancer Research
- Cynthia Bens, Alliance for Aging Research
- Karin Bolte, National Consumers League
- Marc Boutin, National Health Council
- Paul Brown, National Center for Health Research
- Patrick Frey, CDER, FDA
- Sascha Havefield, PhRMA
- Adrian Hernandez, Duke Clinical Research Institute
- Kay Holcombe, BIO
- Maureen Japha, FasterCures
- John Jenkins, CDER, FDA
- Chris Joneckis, Center for Biologics, FDA
- Annie Kennedy, Parent Project Muscular Dystrophy
- Andy Kish, CDER, FDA
- Ian Kremer, LEAD Coalition
- Lisa LaVange, CDER, FDA
- Penny Levin, Teva Pharmaceuticals
- Diane Maloney, CDER, FDA
- Janet Marchibroda, Bipartisan Policy Center

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4 Paul Melmeyer, National Organization for Rare
5 Disorders

6 Theresa Mullin, CDER, FDA

7 Peter Pitts, Center for Medicine and the Public
8 Interest

9 Sharon Terry, Genetic Alliance

10 Terry Toigo, CDER, FDA

11 Pujita Vaidya, CDER, FDA

12 Brad Wintermute, CDER, FDA

13 Janet Woodcock, CDER, FDA

14 Issam Zineh, CDER, FDA

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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,

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

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

12 The panel topics will be as follows: Panel
13 1 will be on "Pre-Market Review and," of course,
14 "Post-Market safety"; Panel 2, on "Regulatory Decision
15 Tools"; finally, Panel 3, on "Administrative
16 Enhancements: Hiring, IT, and Financial."

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

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

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

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

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

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

11 Opening Remarks

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

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

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

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

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

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

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

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

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

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

1 PDUFA.

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

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

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

1 additional resources against it.

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

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

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

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

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

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

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

1 critical program.

2 Thank you very much.

3 Theresa.

4 (Applause.)

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

9 PDUFA Background and Reauthorization Process

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 So our goal is to try to get this package up

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

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

13 After the negotiations are completed, this
14 package that we've put together, this presentation of
15 materials, we publish it in the Federal Register,
16 which is what we did on July 15th, provide at least a
17 30-day period for comment on that package, have a
18 public meeting in which we'll hear the public views on
19 these recommendations, and that's what we're here for
20 today, and that's what we hope to hear and receive in
21 the docket, and perhaps we'll hear from our folks on
22 the webcast as well.

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

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

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

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

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

18 (Applause.)

19 MS. VAIDYA: Thank you, Theresa.

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

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

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

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

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

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

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

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

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

1 of Public Policy with the Alliance for Aging Research.

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

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

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

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

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

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

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

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

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

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

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

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

1 application.

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

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

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

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

3 We also made some changes regarding
4 applications that are filed over protest. So we
5 refuse to file the application based on the quality of
6 the application, but the applicant decides to file
7 over protest. In those cases, the application would
8 be subject to the program performance goals, the 8- or
9 12-month review, but they don't benefit from the
10 additional communication that we see in the program.

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

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

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

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

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

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

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

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

1 letter, and that regards the expectation for a
2 comprehensive and readily located list of manu-
3 facturing facilities.

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

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

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

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

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

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

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

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

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

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

22 So nothing changes from FDA's standpoint,

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 And now I think I will turn it over to Terry

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

3 MS. TOIGO: Thanks, Patrick.

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

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

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

1 highest quality.

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

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

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

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

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

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

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

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

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

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

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

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

5 MS. VAIDYA: Thank you, Patrick and Terry.

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

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

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

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

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

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

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

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

1 drug sponsors.

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

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

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

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

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

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

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

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

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

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

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

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

1 the panelists.

2 Thank you.

3 MS. VAIDYA: Thank you, Cynthia.

4 I'll turn it over to Paul next.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

19 We co-authorized a white paper in 2014 with
20 Frank Sasinowski, of Hyman, Phelps, that showed about
21 67 percent, two-thirds, of orphan therapies enjoyed
22 some sort of flexibility within FDA review. And

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

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

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

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

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

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

9 MS. VAIDYA: Thank you, Paul.

10 Next I would like to turn it over to Sascha.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

20 MS. VAIDYA: Thank you, Sascha.

21 I'll turn it over to Kay now.

22 MS. HOLCOMBE: Thanks very much. BIO

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

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

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

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

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

22 And, finally, enhancements must be pursued

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

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

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

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

1 where we were going to make these things?

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

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

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

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

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

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

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

1 expand our support of this expanded Sentinel System.

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

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

22 So I'm not going to mention any more

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

5 (Laughter.)

6 MS. VAIDYA: Thank you, Kay.

7 And, finally, we have Jeff Allen.

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

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

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

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

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

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

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

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

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

22 And this leads to some of the, I think,

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

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

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

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

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

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

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

22 I hope this is a stepping stone for future

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

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

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

1 just the biomarker that we're interested here.

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

8 MS. VAIDYA: Thank you, Jeff.

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

13 (Applause.)

14 (Break.)

15 Panel 2 -- Regulatory Decision Tools

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

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

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

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

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

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

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

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

1 there.

2 MS. VAIDYA: Thank you, Theresa.

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

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

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

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

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

20 MS. HOLCOMBE: Kay Holcombe.

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

1 DR. MULLIN: Thank you, Pujita.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 So we are basically going to conduct a

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 DR. LAVANGE: Thank you, Theresa.

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

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

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

1 to clarify for sponsors what we expect.

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

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

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

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

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

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

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

1 with, and so forth.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 Thank you.

1 Terry?

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

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

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

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

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

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

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

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

1 disease and health.

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

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

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

13 MS. VAIDYA: Thank you, everyone.

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

18 So first I'll turn it over to Maureen.

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

22 As I mentioned earlier, my name is Maureen

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

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

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

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

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

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

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

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

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

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

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

22 We're supportive of the guidance process

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

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

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

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

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

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

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

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

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

13 MS. VAIDYA: Thank you, Maureen.

14 Next we have Marc.

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

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

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

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

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

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

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

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

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

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

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

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

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

1 put the money there?

2 What FDA and industry have done is they have
3 laid out a map that ends that juggernaut, that catch-
4 22, of, how do you move forward with 21st century
5 science and develop and utilize these tools in a way
6 that will produce higher value products, faster,
7 safer, more tailored to individual subpopulations?

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

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

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

1 your benefit-risk determinations reflect the end
2 user."

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

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

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

22 It's time to figure out, how do we

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

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

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

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

1 effective treatments to market.

2 Biomarkers, surrogate endpoints, already
3 discussed.

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

8 Thank you.

9 MS. VAIDYA: Thank you, Marc.

10 Next we have Annie.

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

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

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

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

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

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

22 So PFDD tools are real-time and incredibly

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

9 And we appreciate the complexity of any
10 review that goes past the PDUFA deadline, and that
11 there is a commitment from all parties to conduct a
12 thorough review as quickly as possible. But what we
13 would ask be considered is that the Agency consider
14 the merits of issuing a brief update 30 days following
15 a PDUFA deadline and every day 30 days thereafter, so
16 30 days after the PDUFA deadline and every 30 days
17 thereafter, until the Agency issues an approval or a
18 complete response letter. We believe that such a
19 cycle would extend the commitment to enhance
20 communications that's included in the draft
21 performance goals.

22 Again, we thank you for this opportunity

1 today and for the ongoing communications.

2 MS. VAIDYA: Okay. Thank you, Annie.

3 And next we have Ian.

4 MR. KREMER: Good morning again, everybody.

5 And I'll just add our thanks on behalf of the LEAD
6 Coalition both to industry and the FDA as well as to
7 the broader stakeholder community for everything that
8 has led up to this commitment letter.

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

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

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

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

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

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

1 dementia and at different stages of dementia, but I
2 hope that those of you from other patient advocacy
3 communities will hear something that resonates for
4 your community in at least some of the examples. So
5 I'm going to run through these pretty quickly, about
6 20 seconds each.

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

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

1 source is, what its manifestations are.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

17 MS. VAIDYA: Thank you, Ian.

18 Next we have Sascha.

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

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

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

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

21 Innovative clinical trial designs.

22 Innovative clinical trial design approaches have the

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

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

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

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

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

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

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

21 Thank you again, and turning it back to you.

22 MS. VAIDYA: Thank you, Sascha.

1 And, finally, we have Kay.

2 MS. HOLCOMBE: Finally we have Kay.

3 (Laughter.)

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

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

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

1 getting therapy to the patient in a timely way.

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

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

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

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

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

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

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

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

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

11 (Laughter.)

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

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

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

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

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

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

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

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

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

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

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

6 MS. VAIDYA: Thank you, Kay.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

10 Thanks.

11 MS. VAIDYA: Thank you, Theresa.

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

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

16 (Lunch.)

17 Panel 3 -- Administrative Enhancements:

18 Hiring, IT, and Financial

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

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

1 trying to stay on schedule here today.

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

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

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

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

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

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

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

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

3 DR. HAVEFIELD: Sascha Havefield, for PhRMA.

4 MS. HOLCOMBE: Kay Holcombe.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 We currently have an IT strategic plan.

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

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

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

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

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

8 I think that's it.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 hope to do to support that.

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

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

18 (Laughter.)

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

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

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

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

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

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

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

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

22 An initial assessment will be done with some

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

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

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

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

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

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

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

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

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

1 little bit better, where we can make some
2 improvements.

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

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

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

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

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

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

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

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

1 establishment fee and a product fee.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 we do exceed a certain amount.

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

7 Thank you.

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

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

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

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

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

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

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

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

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

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

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

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

8 MS. VAIDYA: Thank you, Janet.

9 Next, Cynthia.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

14 MS. VAIDYA: Thank you, Cynthia.

15 Jeff.

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

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

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

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

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

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

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

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

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

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

7 MS. VAIDYA: Thank you, Jeff.

8 Sascha?

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

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

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

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

7 Hiring we just covered.

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

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

1 appropriately funded in the future.

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

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

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

22 So thank you again for the opportunity to

1 participate in the public meeting on behalf of PhRMA.

2 And back to you.

3 MS. VAIDYA: Thank you, Sascha.

4 And, Kay.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

18 MS. VAIDYA: Thank you, Kay.

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

21 Open Public Comment

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

1 the Open Public Comment session.

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

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

14 So we have collected sign-up before the
15 meeting and during the break. We have seven people
16 signed up. So please be respectful for your other
17 colleagues here and stick to the 5-minute time limit.
18 I'll be keeping track of time. Once you approach the
19 4-minute mark, I will try to ask you to start wrapping
20 up, and give you a hard fast stop at 5 minutes.

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

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

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

8 So first can we start off with Peter Pitts?

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

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

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

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

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

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

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

1 impact regulatory decision-making.

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

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

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

1 standard, it means augmenting it.

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

8 Thank you.

9 MS. VAIDYA: Thank you, Peter.

10 Next we'll have Sharon Terry, please.

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

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

18 Genetic Alliance is a large network of
19 10,000 disease advocacy and community organizations,
20 sharing information and resources, developing novel
21 tools, and empowering people to drive research.

22 I also serve as the co-principal

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

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

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

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

1 Every moment, there are patient experiences
2 occurring, but they are not being included in a formal
3 way for evidence. Patients expect that we continue to
4 learn from their experiences to improve the experience
5 of those who walk in their shoes the next time.

6 Unfortunately, that doesn't happen today. PDUFA VI
7 would promote that approach through the emphasis of
8 real-world evidence. My colleague, Adrian Hernandez,
9 of Duke and PCORnet, will address that more completely
10 after me.

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

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

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

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

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

22 We are excited to see PDUFA VI advancing the

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

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

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

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

21 Thank you.

22 MS. VAIDYA: Thank you, Sharon.

1 Next can I have Adrian Hernandez?

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

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

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

1 conditions.

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

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

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

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

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

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

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

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

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

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

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

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

1 participants' voice throughout all of our studies.

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

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

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

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

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

6 MS. VAIDYA: Thank you, Adrian.

7 Next we have Penny Levin.

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

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

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

1 it is, so I'm most appreciative.

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

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

13 Today, one in three of Americans use a Teva
14 prescription medicine. We directly employ more than
15 6,500 Americans and support another 40,000 in direct
16 U.S. jobs with an economic value added of around \$9.2
17 billion in the U.S. last year.

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

1 of our commitment to patients.

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

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

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

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

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

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

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

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

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

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

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

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

5 Thank you.

6 MS. VAIDYA: Thank you, Penny.

7 Next we have Karin Bolte.

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

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

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

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

1 work is made possible by the PDUFA User Fee Program.

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

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

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

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

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

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

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

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

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

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

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

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

1 examining the safety of off-label prescribing to
2 address consumers' lack of awareness and understanding
3 of the practice. We also believe that it is
4 imperative for the FDA to have the staff and resources
5 to ensure that direct-to-consumer drug ads are
6 accurate and not misleading before they reach the
7 public. We strongly believe the FDA should seek the
8 authority to require that all DTC ads undergo review
9 before public dissemination so that misleading
10 information does not reach consumers.

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

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

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

21 MS. VAIDYA: Thank you, Karin.

22 And, lastly, we have Paul Brown.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

9 PDUFA funds should also be used to help
10 monitor direct-to-consumer ads. In 2015, PhRMA spent
11 \$5.4 billion on direct-to-consumer ads. There is a
12 need to carefully review all the ads to reduce the
13 misuse of prescription drugs, such as atypical
14 antipsychotic drugs advertised as if they were
15 antidepressants. PDUFA fees should be used to enhance
16 DDMAC, Division of Drug Marketing, Advertising, and
17 Communications.

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

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

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

20 Thank you.

21 MS. VAIDYA: Thank you, Paul.

22 And that concludes our open public comment

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

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

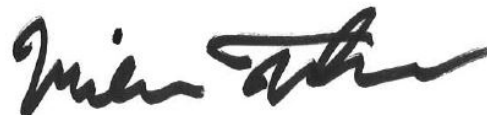
11 (Whereupon, at 1:48 p.m., the meeting was
12 adjourned.)

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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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CERTIFICATE OF TRANSCRIBER

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

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