

U.S. FOOD & DRUG ADMINISTRATION  
PRESCRIPTION DRUG USER FEE ACT  
(PDUFA) REAUTHORIZATION  
PUBLIC MEETING

July 15, 2015

9:01 AM - 2:03 PM

Food and Drug Administration  
White Oak Campus  
10903 New Hampshire Avenue  
Conference Center, Building 22  
Silver Spring, Maryland

Reported by: Natalia Thomas

Capital Reporting Company

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

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

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

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

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



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

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

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

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

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

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

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

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

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

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

7 A few brief housekeeping announcements  
8 before we start. We'll have a 15-minute break at  
9 10:40 and a 50 minute lunch break at noon assuming  
10 I do my job properly. There are food and  
11 beverages available to purchase at the kiosk  
12 outside the room in the lobby and we ask that you  
13 consider pre-ordering your lunch before 11 o'clock  
14 so that we -- because we only have a short time  
15 for lunch and we can -- that will help crowd  
16 management. And so the food and beverages, as  
17 most of you have been here before know, there's  
18 the kiosk outside the room. And then restrooms  
19 are down the hallway in the lobby on the left. So  
20 that's it for housekeeping.

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

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

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

1 of Pluto.

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

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

1 41 novel new drug products were approved with 17  
2 of these being approvals for orphan drugs, the  
3 highest annual total ever.

4           And FDA really continues to meet or  
5 exceed nearly all of our review performance goals  
6 that are central to PDUFA process and outcome  
7 deliverables. In addition to that, first cycle  
8 approval rates for NMEs and BLAs have been  
9 steadily trending upward towards historic levels;  
10 73 percent of all novel products and 93 percent of  
11 priority novel products have been approved in the  
12 first cycle during PDUFA V. We'd like to believe  
13 that this is due, at least in part, to the success  
14 of PDUFA V NME BLA review program, which is an  
15 innovation from the last PDUFA reauthorization  
16 that facilitates early communication between  
17 review teams and sponsors and I think has been one  
18 of the keys to success.

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

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

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

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

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

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

6           (Applause.)

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

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



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

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

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

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

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

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

1 That's really exciting.

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

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

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

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

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

17           (Applause.)

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

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

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

19           So before the passage of the first PDUFA  
20 in 1992, you know, drug lag was a big problem.

21 The U.S.

22           was behind Europe in many areas and

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

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

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

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

1 are so we say the devil is in the details.

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

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

22           And finally, we've focused more in this



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

9           This is just a quick overview of the fee  
10 structure. There are three pieces -- three  
11 components of fee. It's divided into a full  
12 market application, payments, establishment fees  
13 for the finished dosage, foreign facilities, and  
14 product fees. The total revenues in this current  
15 fiscal year are estimated to be on the order of  
16 \$800 million dollars, and that last is just a  
17 breakout of those -- the amount of fee per  
18 submission or per item in the current year, so  
19 it's a big program.

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

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

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

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

1 multiple scientific disciplines need to be  
2 involved. So the pink part of the bar you see  
3 here is the internal goals that we set to modulate  
4 and have this process that's complex but needs to  
5 be because the products are becoming increasingly  
6 complex in order to orchestrate this to get a  
7 final decision or to get the external goals met.  
8 So all told, we have -- our reviewers are  
9 following as an organization on the order of  
10 16,000 goals in order to just keep moving things  
11 along and getting that complete process with all  
12 the necessary input and vetting in the timeframes  
13 that we've committed to. So there's a lot of  
14 organization that goes on behind the scenes to  
15 make this happen.

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

1 to date.

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

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

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

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

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

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

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

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

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

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

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

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



1 efficient.

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

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

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

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

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

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

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

22           MS. TOIGO: Thank you, Theresa.

1 (Applause.)

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

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

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

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

4 first.

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

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

1 will help crack that problem or make progress  
2 there.

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

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

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

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

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

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

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

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

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



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

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

22           MS. TOIGO: Thank you, Allan.

1 (Applause.)

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

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

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

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

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

1 on numerous policy issues including child labor,  
2 privacy, food safety, medication safety, etcetera.  
3 From the first Pure Food and Drugs Act passed in  
4 1906 which NCL was very much a part of drafting  
5 and advocating for to the more recent FDA  
6 Modernization Act, NCL has been working alongside  
7 the Agency to ensure the public is adequately  
8 represented and protected and that our medications  
9 are safe and effective.

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

1 than the average consumer.

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

8            A patient suffering from a serious  
9 illness is far more likely to take on greater risk  
10 to get the benefits from a specific treatment.

11 This difference in risk assessment between  
12 patients and consumers is critical when  
13 considering the policy implications in this sixth  
14 reauthorization of PDUFA.

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

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

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

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

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

7 More recently, according to FDA's Fiscal  
8 Year 2014 Report to Congress, as of September  
9 30th, 2014, the FDA had completed over 1,400 view  
10 actions and met or exceeded the majority of its  
11 performance goals for Fiscal Year 2014.

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

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

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

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

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

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

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

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



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

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

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

22 A 2006 study analyzing prescribing

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

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

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

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

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

16           A 2013 content analysis of false and  
17 misleading TV ads found 33 percent of prescription  
18 and non-prescription drug ads were objectively  
19 true; 57 percent were potentially misleading; and  
20 10 percent were false. So consumers are  
21 continually exposed to these ads.

22           We think it's imperative that the FDA

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

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

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

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

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

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

6 MS. TOIGO: Thank you, Sally.

7 (Applause.)

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

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

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

1           So before getting into our goals for  
2 PDUFA VI, I'd first like to provide a bit of an  
3 introduction to NORD and to rare diseases. So  
4 just a few facts about rare diseases. There are  
5 an estimated 7,000 known rare diseases; 1 in 10  
6 Americans has a rare disease, so that is 30  
7 million Americans in the aggregate. And a rare  
8 disease is defined as a disease that affects  
9 200,000 people or fewer within the United States  
10 in any given year. Two-thirds of people with rare  
11 diseases are children and 80 percent of rare  
12 diseases have a genetic component. While there  
13 are 7,000 known rare diseases, there are only  
14 approximately 450 orphan therapies treating about  
15 350 diseases so, obviously, there is much more  
16 work yet to be done.

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

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

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

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



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

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

1 of drugs and biologics.

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

7 Our second priority is to strengthen and  
8 incorporate the patient voice throughout the drug  
9 development process. I think this starts with  
10 patient-focused drug development. We were very  
11 supportive of the passage of the patient-focused  
12 drug development piece within the 2012 FDASIA bill  
13 and we have been very pleased with the program  
14 since. We've been at or I personally have been at  
15 most, if not all, of the patient-focused drug  
16 development meetings for patients with rare  
17 diseases. And I do know that the patients have  
18 come aware very pleased with the meetings and that  
19 they have been very happy to participate within  
20 the meetings.

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

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

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

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

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

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

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

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

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

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

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

17           Fourth, we also want to ensure that rare  
18 disease patients have access to off-label  
19 therapies. Of course, the vast majority of rare  
20 disease patients are treated off-label since only  
21 350 diseases that rare diseases have an on-label  
22 therapy. And so we want to ensure that therapies

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

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

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

17           (Applause.)

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

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



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

5 (Chorus of good mornings.)

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

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

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

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

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

22 I'm here from the National Health

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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



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

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

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

1 Apple phone.)

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

4 (Whereupon, a showing of approximately  
5 30 percent of the audience indicate in  
6 the affirmative positive to having  
7 Samsungs.)

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

11 (Whereupon, a showing of approximately  
12 10 percent indicate in the affirmative  
13 to having a Blackberry.)

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

16 (Laughter.)

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

1 of the end user.

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

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

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

6 (Applause.)

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

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

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

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

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

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

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

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

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

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

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

1 within drug development.

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

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



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

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

1 accelerating the development without compromising  
2 standards.

3           While the breakthrough designation has  
4 created positive enhancement, it's also helped  
5 raise the awareness of important challenges that  
6 still exist across all of drug development.

7 Perhaps these are areas that could be considered  
8 further in terms of the user fee reauthorizations.

9 These could include enhancing the interactions  
10 between centers to further align administrative  
11 processes for drugs that are developed with a  
12 companion diagnostic. In terms of breakthrough  
13 designations, over a third of the drugs designated  
14 contain a pharmacogenetic marker associated with  
15 their use, so this is becoming increasingly  
16 important.

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

22           And finally, there may be opportunities

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

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

8 (Applause.)

9 MS. TOIGO: (Inaudible.)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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



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

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

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

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

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

1 performance outcome measures, observer reported  
2 outcome measures, and clinician reported outcome  
3 measures.

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

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

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

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

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

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

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

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

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

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

13           (Applause.)

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

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

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

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

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

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



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

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

22           Specifically, FDASIA, the authorizing

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

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

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

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

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

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

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

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

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

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

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

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

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

22           Again, I'd like to thank FDA for the

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

10 MS. TOIGO: Thank you, Maureen.

11 (Applause.)

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

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

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

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

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

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



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

8           Generally speaking, APhA believes that  
9 progress has been made on PDUFA V's goals. In  
10 2012, we commented on several aspects of PDUFA V  
11 including drug shortages, REMS, biomarkers and  
12 pharmacogenomics as well as the Sentinel  
13 initiative. We appreciate the progress we have  
14 seen in these areas. However, as we all know, and  
15 many of us that make a living with healthcare,  
16 it's not static and due to the changing landscape  
17 and technological advances, certain facets of some  
18 of these areas may need to be revisited.

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

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

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

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

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

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

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

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

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

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

22           However, pharmacists face significant

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

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

1 policy areas.

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

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

22                   (Applause.)

1 MS. TOIGO: Thank you, Stacie. James.

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

8 The American Academy of Pediatrics is a  
9 non-profit professional medical organization of  
10 over 64,000 pediatricians including primary care  
11 pediatricians as well as medical and surgical  
12 pediatric subspecialists. Our mission is  
13 dedicated to the health of all children from  
14 infancy through adulthood, and it's in pursuit of  
15 that mission that AAP has led efforts to increase  
16 the number of drugs studied in children since the  
17 publication of its seminal policy statement in  
18 1977 calling for a dramatic shift in how we  
19 approach pediatric drug development in this  
20 country.

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

1 Pediatric Research Equity Act, PREA, have truly  
2 changed the way pediatrics are practiced in the  
3 United States. Prior to BPCA and PREA, upwards of  
4 80 percent of drugs used in children were not  
5 studied in children and were, therefore, not  
6 labeled for their use. Now, today, that number is  
7 much closer to 50 percent. So we've certainly  
8 come a long way. It's a mark of success but we  
9 have a long way to go.

10 BPCA is a voluntary incentive of six  
11 months of additional marketing exclusivity for  
12 conducting FDA-requested studies in children, and  
13 PREA is a premarket pediatric studies requirement  
14 that applies to new drug applications as well as  
15 supplements. Combined, BPCA and PREA have led to  
16 580 labels changed with new pediatric information.

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

22 So in terms of the Prescription Drug



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3           Next, pregnant and breastfeeding women:

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

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

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

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

20                   (Applause.)

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



1 College of Cardiology.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

9 (Applause.)

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

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

22 PhRMA is a trade association

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

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

22           The FDA's mission is to protect and



1 promote the public health by ensuring the safety,  
2 efficacy, and quality of human drugs and  
3 biologics. Biopharmaceutical companies share the  
4 Agency's commitment to serving the public health.

5 We do this by researching safety, efficacy and  
6 quality of human drugs and biologics.

7 Biopharmaceutical companies share the Agency's  
8 commitment to serving the public health. We do  
9 this by researching, developing, manufacturing,  
10 and delivering innovative, safe, and effective  
11 medicines to treat devastating illnesses such as  
12 cancer, diabetes, and Alzheimer's disease.

13           Our understanding of many diseases has  
14 increased tremendously in recent years and the  
15 potential public health implications of the  
16 science we utilize have never been more promising.

17 With more than 7,000 medicines in development  
18 globally, biopharmaceutical researchers are  
19 working to turn potential treatments into FDA-  
20 approved medicines that will help patients. This  
21 work not only benefits patients directly but the  
22 U.S. economy as a whole. Working with scientists,

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

6           PhRMA members have invested more than  
7 half a trillion dollars in research and  
8 development since 2000 including an estimated  
9 \$51.2 billion dollars in 2014 alone. This  
10 investment represents the largest R&D commitment  
11 of any business sector in the U.S.

12           Only one out of thousands of promising  
13 preclinical molecules and less than 12 percent of  
14 candidate medicines that enter phase one clinical  
15 trials will ultimately be approved by the FDA.

16 This attrition rate is one reason that the  
17 investment in R&D is so great in our industry.  
18 Thus, we assume great risks in order to deliver  
19 great benefits to patients. It follows then that  
20 our industry has a tremendous stake in  
21 facilitating timely science-based FDA regulatory  
22 review and approval of safe and effective

1 medicines to address patients' needs.

2 PDUFA has played a critical role in  
3 bolstering the FDA's ability to regulate safe and  
4 effective medicines for patients. PDUFA was  
5 created in response to a perilous bottleneck of  
6 new drug approvals in the late 1980's and early  
7 1990's that left patients waiting and sometimes  
8 dying while an understaffed and underfunded FDA  
9 struggled to review new drug applications.

10 As you've already heard earlier today,  
11 in 1992, Congress passed the first Prescription  
12 Drug User Fee Act to meet urgent patient needs for  
13 timely approvals of life-saving medicines. For  
14 more than 20 years, PDUFA has helped the FDA  
15 fulfill its central mission to protect and promote  
16 the public health by allowing the Agency to keep  
17 pace with the rapid increase in the number and  
18 complexity of innovative drugs and biologics  
19 entering the review pipeline.

20 The PDUFA program has enabled FDA to  
21 hire additional staff to review applications for  
22 new drugs and biologics. In 1998 -- in 1989 --

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

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

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

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

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

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

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

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

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

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

3 PDUFA's 23-year history has paralleled  
4 the most productive and innovative generation of  
5 new drug development. From novel vaccines to  
6 breakthrough medicines and target therapies, the  
7 past two decades have seen a revolution in  
8 innovative medicines addressing unmet medical  
9 needs. FDA can be proud of its leadership and  
10 helping biopharmaceutical companies deliver these  
11 therapeutic advances to the public by vigilantly  
12 watching out for their safety. The lives of  
13 countless children, adults, and aging Americans  
14 have been enriched and extended by the hundreds of  
15 novel therapeutics that have passed through the  
16 FDA's regulatory review programs since PDUFA's  
17 inception in  
18 1992.

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



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

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

15 MS. TOIGO: Thank you, Sascha.

16 (Applause.)

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

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

1 toward the authorization of PDUFA VI.

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

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

1 approval rates.

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

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

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

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

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

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

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

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

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

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

1 communication.

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

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

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

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



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

6 Thank you.

7 (Applause.)

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

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

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

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

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

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

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

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

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

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

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

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

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

22           So we believe there needs to be a focus.

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

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

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

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

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

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

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



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

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

1 forward. Thanks very much.

2 (Applause.)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

22                   And then finally, in this very quick

1 last point is moving beyond PDUFA V, this idea of  
2 improving innovation measurement. Significant  
3 challenges exist in compiling data on the actual  
4 drug approval process itself. For example, policy  
5 analysts might say, oh, you know, this year we had  
6 41 NMEs approved, last year we had less than that;  
7 therefore, we're doing better. We might be but  
8 what might also be important to understand is are  
9 those products, on average, addressing unmet need.  
10 Are they really addressing and bringing new  
11 innovation to our healthcare system?

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

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

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

22 MR. DANIEL: And so -- and that actually



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

3 MS. TOIGO: Thank you very much.

4 (Applause.)

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

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

14 So just as a general background, I'm  
15 going to focus very specifically on two issues,  
16 the first of which is the filing review, the extra  
17 60 days that Commissioner Mullin told you about  
18 earlier today and -- sorry, not Commissioner --  
19 Dr. Mullin -- sorry. PDUFA 2012, PDUFA V requires  
20 that the FDA complete a filing review within 60  
21 days from the NDA filed. And that's sort of  
22 associated with a set of concerns that arose in

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

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

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

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

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

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

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

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

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

6

7

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

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

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

3           What is has done perhaps is to have led  
4 to an increase in quicker review s. I can't say  
5 this is causal but if we take a look at standard  
6 and/or priority and non-priority NMEs and BLAs and  
7 we just code for one fact, whether they were  
8 approved more than 30 days ahead of the goal date,  
9 right, which is by definition, by the way, first  
10 cycle approval, we see the odds for PDUFA 2012  
11 compared to the last two years of PDUFA IV about  
12 2-1/2 times increase in the odds of a very quick  
13 approval defined that way. If we control for  
14 review cycles, it actually goes up. So actually,  
15 if we control for the facts that many of these are  
16 non or first cycle reviews, we actually get an  
17 odds ratio of about three. In other words, in  
18 many cases, more time -- I don't want to say leads  
19 to; that's a little bit misleading on my part --  
20 it's associated with not necessarily causal of  
21 these quicker reviews.

22           So, to conclude, the experience is early

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

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

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

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

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

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

22 And what I want to do in my remaining



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

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

1 decades approximately, building a database of 774  
2 prescription therapeutics of which one-third were  
3 designated by the FDA as first-in-class agents and  
4 looked at the application of these accelerated  
5 designations to these products. And what we find  
6 is that we see a statistically significant  
7 increase over time in the mean number of  
8 designations granted from the beginning of about  
9 .6 or about .7 to over 1.3 designations per drug  
10 and an increase -- also a statistically  
11 significant increase in the proportion of newly  
12 approved therapeutics that are granted at least  
13 one of these four designations.

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

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

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

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

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

14                   But nevertheless, the second study that  
15 I want to tell you is this -- is what the  
16 implications are of giving a product a  
17 breakthrough designation and in order to study  
18 this, we did a randomized national sample of over  
19 1,000 board certified internists and internal  
20 medicine specialists. We got 718 respondents for  
21 a 62 percent response rate and asked them four  
22 questions. The first three questions are what's

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

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

1 identify that high-quality breakthrough drugs do  
2 not need to be safer than currently approved

3 (inaudible)

4 So then our final question is we asked them  
5 imagine your patient has a serious medical  
6 condition for which there has been no effective  
7 treatment, the FDA approved two drugs, both are  
8 oral tablets, blah- blah-blah, which would you  
9 choose first, Axabex, a hypothetical drug, and FDA  
10 designated breakthrough drug, or Zykanta, a drug  
11 with early promising study results but which has  
12 not been show to improve survival or disease-  
13 related symptoms, which is the definition of a  
14 breakthrough drug. Obviously, since these two  
15 things are interchangeable, we would expect about  
16 50/50. What do you think we saw? Ninety-four  
17 percent of physicians agreed that they would  
18 choose Axabex over Zykanta.

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

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

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

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

3 MS. TOIGO: Thank you, Dr. Kesselheim.

4 (Applause.)

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

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



1 approved. Witness, the hepatitis C events.

2 Let's begin with who gets this drug.

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

13 There are various possible approaches.

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

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

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

22           MS. TOIGO: Thank you. And our last

1 speaker is Rena Conti.

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

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

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

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

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

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

1 over time.

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

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

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

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

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

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

5 MS. TOIGO: Thank you.

6 (Applause.)

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

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



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

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

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

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

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

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

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

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

15 At this time, nearly four-fifths of NMEs  
16 or BLAs are approved on the first cycle and so I  
17 think that's very good for everyone. Most novel  
18 products are receiving, as we heard from some of  
19 our speakers, some sort of expedited review. And  
20 2014 was really a good year for novel rare disease  
21 approvals with 17 approvals for targeted rare  
22 diseases, which is very good news for that

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

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

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

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

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

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

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

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

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

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

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

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

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

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

11           (Applause.)

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

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



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

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

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

1 MR. SUN: That's okay. Okay, great.

2 I'm going to take up all the minutes that I can  
3 get here.

4 MS. TOIGO: You have five.

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

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

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

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

22           FDA also released a risk-based

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

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

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

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

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

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

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

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

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

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

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



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

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

7 MS. TOIGO: Thank you, Stephen.

8 (Applause.)

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

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

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

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

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

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

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

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

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

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

1 (Applause.)

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

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

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

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

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

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

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

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

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

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

22 IPEC-Americas is not looking for an



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

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

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

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

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

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

1 provide these comments today.

2 MS. TOIGO: Thank you, David.

3 (Applause.)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

12 MS. TOIGO: Thank you, Paul.

13 (Applause.)

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

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



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

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

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

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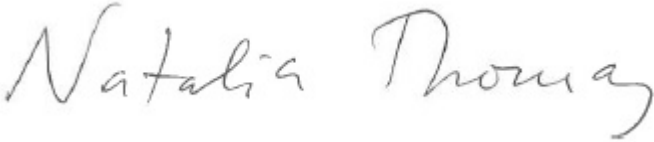
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I, NATASHA THOMAS, the officer before whom the foregoing proceeding was taken, do hereby certify that the proceedings were recorded by me and thereafter reduced to typewriting under my direction; that said proceedings are a true and accurate record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



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State of Maryland

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