U.S. FOOD AND DRUG ADMINISTRATION

PUBLIC MEETING ON THE RECOMMENDATIONS FOR PRESCRIPTION DRUG USER FEE ACT (PDUFA) REAUTHORIZATION

Tuesday, September 28, 2021

9:00 a.m.

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Page 2

A P P E A R A N C E S

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Page 3

C O N T E N T S

Page 4

Page 5

P R O C E E D I N G S

MR. THOMPSON: Apologies for one second, we're having so -- I'm sure you can tell that there was some issues with the audio. We're going to see if we can get that back.

All right. Well, looks like we're having some issues with the audio there. What we're going to do is end up posting a full video of Janet's remarks -- Dr. Woodcock's remarks to the website, so you'll be able to see them there. Apologies for that.

And let's move on to Andrew Kish, who will be providing the background of the PDUFA program where we are in the reauthorization process, and quick overview of the proposed enhancements. And, hopefully, it will be done in a more crystal clear audio fashion.

PDUFA Background and Overview

MR. KISH: Thank you, Graham. Good morning, everyone. Sorry about the technical challenge there. There's -- have any problems hearing me please -- please let me know. We aren't going to minimize folks on video. Make sure everyone has enough bandwidth to hear us and see us during the presentation today.

So, I'm going to give a really quick

Page 6

background on PDUFA and the reauthorization process. And those of you who were -- had been following this since it started, which is last summer with our initial kickoff meeting, some of this going to look very familiar.

We will go ahead and go to the next slide. We can jump to the next one. Okay. So, just really brief background on the history of PDUFA. PDUFA is the oldest user fee program at FDA. And it started in 1992 and it has evolved quite a bit. It came about initially, really just to add funds for premarket review. And this was really helping with a substantial backlog we had at that time where we could set additional funds that would allow us to hire staff, to have capacity, to set predictable timelines, to make decisions on applications.

As we move into PDUFA II, they were added goals and shortening of review times. And then as we got into PDUFA III and PDUFA IV, really start to see the program move into the post-market area, particularly in PDUFA IV where there's a focus on modernizing post-market safety system.

PDUFA V introduced the small increase to the base funding review enhancements to increase communications and sponsors, the program, the folks are

Page 7

familiar with the program and strengthened regulatory science and post-market safety.

As we moved into VI, which is what we're currently in right now, there's a focus on modernizing the user fee structure, on enhancing HR and financial management, creating a new capacity planning capability and enhancing our use of regulatory tools via benefit-risk, patient-focused drug development, complex, innovative trial designs, model informed drug development, and a number of other enhancements, including exploring RWE in regulatory decision-making.

That's the very brief background of PDUFA. And as folks know today we're presenting the recommendations for enhancements to PDUFA VII.

You can go to the next slide. A little bit on the timeline. Graham did touch on this on his opening remarks. But, as we started this process last summer with the public announcement of the initial meeting -- the public meeting to kick off the negotiation process.

We then engaged in technical negotiations between industry and FDA, starting in September that ran through February and this also included a parallel process were we held -- FDA held meetings with stakeholders who signed up for the stakeholder engagement process.

Page 8

And then through March of this year, and September, there's the clearance process for -- on the government side, which includes FDA, HHS, and OMB finalization of the package, including briefing the two congressional committees responsible for heavily reviewing this proposed legislation package. And then where we are today -- the final public meeting.

Today's public meeting, as Graham mentioned, is for us to share proposed enhancements and to hear your feedback through the public comment period. And as also noted, the public docket is open, we encourage you to submit your comments through the docket. That will remain open through nearly the end of October.

After we reviewed the dockets comments and feedback from this public reading, we will then make any changes as necessary to the proposed commitment letter, and then we have a statutory deadline to transmit that to Congress by January 15th of next year. And from January 15th to September 30 of 2022, it is with Congress for consideration and anticipated passage of reauthorization. As currently noted -- as previously noted, the current PDUFA program will sunset in September 30, 2022.

You can jump to the next slide. And here's the statute prepared (inaudible) that we are at that

Page 9

fourth step public review of recommendations, as I mentioned on the previous slide.

We can go to the next slide. So, give a really quick overview of really the recommendation sections, then we'll have lead negotiators for those sections in FDA, present an overview of the highlights of those particular sections and then have our industry colleagues from pharma and bio provide their input and thoughts after the presentation of each section.

Okay. So, there are a number of areas of proposed enhancements. And the commitment letter, I'm sure those of you, who have looked through it are familiar with this. Also those of you who have followed our public meeting minutes that we posted throughout the entire negotiation process. And I'm not sure if you heard it in Janet's opening remarks, but there is over 100 meeting minutes posted during the process.

We have structured the presentation today that closely follow how those meeting minutes were posted in the groups, so you can follow those topic areas if you have a particular interest. That includes CBER review support. So that's heavily focused on enhancing CBER's capacity, particularly around cell and gene therapies.

Pre-market, sort of introducing new approaches

Page 10

to improve the human drug review process, including new pilot programs. Regulatory decision tools; post-market; a new area for PDUFA -- chemistry and manufacturing controls, particularly around facilitating manufacturing readiness and use of innovative manufacturing technologies. And also partially new introduction to PDUFA is digital health -- digital health and informatics variant. We'll have Mary Ann Slack provide the overview; and finance; and then hiring and retention.

So we have a lot to cover. And I will go ahead and turn it over to Chris Joneckis from CBER, who will be presenting the CBER Review Support.

MR. THOMPSON: While we're transitioning, I'd just like to let people know that, yes, we will be making these slides available after the meeting along with the recording and the transcript of the meeting. Thanks very much.

And Chris, it looks like your slides are loaded. So we'll turn it over to you and our -- we can move the slides yourself or you can request control if you'd prefer.

CBER Review Support Proposed Enhancements

Page 11

MR. JONECKIS: Good morning, Graham. Can everyone hear me?

MR. THOMPSON: Yes, we can.

MR. JONECKIS: Great, thank you. Good morning. My name is Chris Joneckis. As the slide indicates I was the lead for the CBER Review Support Group and I also served as the CBER lead for user fees, including PDUFA.

So, I think everyone is well aware that there has been a substantial and sustained increase in activity in the cell and gene therapy arena, especially over the past few years. And this has clearly been reflected in increased numbers of meetings, IND submissions, BLA submissions and evidence that, you know, as more additional products are approved, there's a maturing field, so there's additional post approval work and activity.

As an aside, this actually increase continues to be maintained throughout COVID as well. This increased demand has far exceeded the staff numbers and staff capacity that CBER felt was needed to provide for the -- support for the cell and gene therapy program to the ability that we would prefer, especially to support and grow the cell and gene therapy program as we would like.

Page 12

So, during negotiations, industry and CBER both recognized that there was need for an additional support for the cell and gene therapy program. And in discussing this, we determined that there needs to be a more comprehensive approach to address what CBER wanted to achieve, and of course, what industry wanted to achieve and felt was necessary to have a very strong and sustained cell and gene therapy program.

Slide please. So, one of the major outcomes of this -- of PDUFA in this field is that there was a significant increase in staff capacity and capabilities in CBER to support that regulation and review of the cell and gene therapy products. There is a substantial number of staff to support the cell and gene therapy review in the order of approximately 160 additional staff that will be joining over the course of the PDUFA VII.

The majority will be involved in, of course, the cell and gene therapy review and regulation and they'll be in our office -- OTAT -- Office of Tissues and Advanced Therapies and other review offices that directly support that review.

There will be a limited -- very limited number of staff that will support other related functions related to things of hiring, communication and such, as

Page 13

well some regulation policy, and so on and so forth that is necessary to provide both a direct and indirect support for the review of cell and gene therapy products.

This staff capacity will clearly allow us to meet these increasing challenges and demand in this evolving and rapidly growing field such that we can spend additional time when existing reviews, meetings, growing the program, and also there's other indirect activities to provide additional regulatory support and outreach. Things such as, you know, webinars, doing additional recorded training, to facilitate both industry and stakeholder education and interactions, which again occurs both nationally and internationally, additional policy developments and such.

In the field of cell and gene therapy, I think, it's important to understand that there's a wide variety of industry -- industries that are representative. They are of all sizes from small to large and well established industries, and a lot of newer industries as well who perhaps don't have as much regulatory expertise -- those who are well established and therefore we need to provide support across the board.

So with that increase in amounts of staff that

Page 14

we would have, it's important -- it was felt important by both CBER and the industry negotiators that we provide support to integrate and onboard that large number of new staff. And so, to that end, there are -- some of the PDUFA funding will be used to look at integration and onboarding, making sure we have an appropriate change management program, as well doing an assessment of the office, OTAT, for example, and other structures within CBER to see what -- how it was the best way to efficiently organize those. And also some additional funding to provide an assessment of the program, how we communicate, and so on and so forth.

A key part is to make sure that we have -- facilitate an enhanced communications. So, we will continue the interactions that we've had with our other stakeholders continue, for example, public-private partnerships, national and international venues. Also, internal outreach as well through the wide variety of cell and gene therapy applicants that we have.

We're also taking some of that money to do an internal assessment as well to -- as part of the CBER modernization program to evaluate, streamline and harmonize our various cell and gene therapy processes and procedures, how we interact with people, how we communicate, in an attempt to enhance the regulatory

Page 15

actions and reduce that burden, basically to take a look at our optimization of our efficiency as well.

A peer part of this is to enhance regulatory consistency and additional -- hopefully, provide additional review standards, reduce any kind of regulatory burden, optimize our efficiency, and so on. Again, this has to occur in the context of a rapidly developing and evolving field, so it's very challenging to do so. Also, we will continue again our external collaborations to participate in various public-private partnerships, internal interactions, and so on.

We will also continue to have those discussions, as the Agency is having discussions on the use of existing approaches and evaluating potential new approaches. So discussions on surrogate endpoints, real-world evidence, complex innovative designs, natural history studies, for example, in the clinical area, as well as exploring new approaches for how we can obtain efficiency and safety information.

And especially in the cell and gene therapy area, it's important to look at that for rare and ultra-rare diseases, because there are a lot of those disease populations that are looking at cell and gene therapy as a potential therapeutic core.

We have not been waiting for PDUFA VII, we

Page 16

have been starting a lot of the assessments, initiating changes, how we're going to be doing hiring with the limited resources that we have available. And so we've been making quite a bit of progress on that.

As part of the field, CBER and industry both agreed on a series of meetings to explore the challenges cell and gene therapies and how we can meet them. This is a continuation of a lot of the meetings that we've had over the years with stakeholders that have been funded, in part, by base funding as well as PDUFA funding.

So, some of the major ones that we have agreed to and are described in the PDUFA commitment letter would be a patient focused drug development meeting in which we can better understand patient perspectives on gene therapy studies and products.

That things -- so we would explore areas like patient and caregiver's level of understanding and expectations regarding the benefits and risks of their cellular and gene therapies, which would be their involvement in the clinical study design and execution, exploring patient experience and patient preference data, looking at existing tools or considering the need to develop new ones, and so on.

Another area is looking at novel approaches.

Page 17

What types of various novel approaches can be used to determine efficacy and safety data. Again, there is a large emphasis on small or ultra-rare populations in the cell and gene therapy field. So, we have been looking at different ways of how we can challenge that and we'll explore those in stakeholder meetings with industry academics, patient group, so on.

Part of the novel approaches as in this rapidly evolving field, we are faced with many challenges, and so we'll be looking at trying to take a more Q&A approach to keep documents updated to reflect some of our current thinking on challenges -- common challenges that lot of individuals in this area face. We also, therefore, also look at exploring approaches to capturing that post approval safety and efficacy data for both the cell and gene therapy product.

Another area in which we'll be having more public discussions will be in the expedited programs area. I think most people are probably aware in this field of the RMAT program, the regenerative medicines advanced therapies programs.

We are going to be -- have been looking at reviewing and updating our experience gained from that since its passage several years ago, and we'll be having additional discussions on how we can use --

Page 18

potential use, real-world evidence, accelerated approval. And then in particular for cell and gene therapy is making sure that CMC areas are ready for applications. This has been again particularly challenging for cell and gene therapy products, because they're really new and novel manufacturing approaches and challenges that have to be overcome.

And the last area in the support for public meetings will be in leveraging knowledge. This was of great interest to our Industry partners, and they wanted to understand how is it possible that they can access nonproprietary knowledge in multiple areas. We will continue our advancement of standards, for example, in various areas that we have been emphasizing over the past few years. And how can manufacturers and other Industry individuals can leverage internal prior knowledge and public knowledges in multiple areas -- preclinical, clinical, and CMCs.

So, all of these activities that we've discussed involve public-private partnerships, involvement of all stakeholders in various public meetings. And the information gained from these types of meetings can be used to inform subsequent thinking and development of guidances.

And, of course, as you will hear later today,

Page 19

all the sections of PDUFA also do support the cell -- the cell and gene therapy program as they support other CBER products as well that are considered (inaudible) products of course.

Now turning to Allergenics, next slide please Graham. The other major part in this area of support for CBER biologics is the incorporation of new allergenic extract products into the PDUFA program and the PDUFA resources will provide that additional capability to review these products under the PDUFA paradigm.

Since PDUFA's inceptions, the allergenic extract products have previously been excluded in the statute. It's important to recognize that the most of our new allergenic products that are under development are targeted food allergies, such as the recent approvals for peanut allergy treatments.

So allergies to foods are increasing, especially among children, and so it's very timely that getting the PDUFA resources to support this program will be very beneficial both to CBER, to industry and to the patients that are targeted for these allergenic extract products.

So, basically, with the start of PDUFA VII on October 1st, they will generally be included in user

Page 20

fees. So, basically new INDs, BLAs, and so on, will be included in those user fees.

The third bullet point here, allergenic extract products licensed before October 1, 2022 and standardize allergenic extract product submitted pursuant to a notification to the applicant from the secretary regarding the existence of a potency test that measures the allergenic activity of an allergenic extract product licensed by the applicant before October 1, 2022, would remain excluded from PDUFA.

So, what that that says basically is that, for existing allergenic products that already have been -- have applications submitted, if you will, they will continue to be regulated as non-PDUFA products. And also have the ability, occasionally we will standardize allergenic extract products, which means that we issue a specific potency standard and all the other allergenic products out there have to determine their potency relative to that product. Those will not be different products and therefore no fees will accrue -- will accrue.

Of course, with these newer allergenic products, again, that are mostly targeted at food allergies, all the performance goals, procedures commitments, will apply to allergenic products that

Page 21

include too -- excuse me, that includes the PDUFA products as well. And these PDUFA resources for these newer products will allow for a more timely review of these INDs, BLA submissions, post approval submissions that were previously reviewed on a resource dependent basis, as well.

And I think this overall approach to allergenic products strikes a really good balance in the regulation of allergenics and meets both the needs of CBER's and industry and the various patients that have these products.

So, with that, thank you for your attention this morning.

MR. THOMPSON: Thanks very much, Chris. Now we are going to turn it over to Cartier and Lucy from Industry to give some Industry comments.

MS. ESHAM: All right. Good morning, everybody. I'll do my audio check. Is this coming in clear?

MR. THOMPSON: I can hear you loud and clear.

MS. ESHAM: Great, thank you. And thank you Chris for that great overview. And I'm just going to underscore a couple of things for the audience.

Again, Chris did an excellent job covering the points of the agreement. But I think it's important to

Page 22

note and underline that there was significant alignment going into these negotiations that there was -- that there was a need to focus on CBER's resources given the high -- the present high -- increased volume and demand being put on CBER and that, that we sort of projected and predicted that will be needed over the course of the next PDUFA cycle.

And so, again, I think the agreement reflects appropriately the significant need that we wanted to resolve. And with, in the commitment, there is going to be -- the ability of CBER to bring on a significant number of staff to address that increased volume and demand. And we did want to make sure they could get that as soon as possible. So, we do expect the onboarding -- a majority of the onboarding to be happening in the first year or two.

Given that, as Chris mentioned, you know, we discussed a lot about the importance of ensuring that with that onboarding, there was resources provided for CBER to make sure that they could do change management and onboard those new staff in a way that will continue CBER to be able to maintain a culture of scientific engagement and optimal -- optimal scientific dialogue.

Additionally, there was a lot of discussion to make sure that CBER had the resources they need to best

Page 23

enable bio and pharmaceutical companies to continue to modernize how they're approaching drug development, including for cell and gene therapies. And so, we wanted to make sure that there were resources and ability to advance regulatory -- to better understand regulatory thinking, advanced regulatory thinking, and create a shared understanding about how to utilize things such as patient perspective data, real-world evidence, innovative clinical trial designs. And as Chris mentioned, to be able to be engaging with key stakeholders and scientific leaders throughout our community to even explore new ways to assess benefit and risks in cell and gene therapies.

This also included -- as Chris mentioned, there will be appropriate focus on the unique needs of small and ultra-rare diseases that is of particular input for many of our cell and gene therapy, treatments.

And lastly, I just want to underscore there's also going to be some engagement and dialogue and guidance on things like CMC readiness. And how can we think about leveraging prior knowledge across therapeutic areas for non-clinical, clinical knowledge, CMC knowledge. And I think all of that will really serve well to continue to advance the field and ensure

Page 24

that we have effective and efficient review processes over the course of the next PDUFA cycle.

And, lastly, I'll just note that we also had some discussions that, there are oftentimes if there are frequently asked questions that everybody is asking the same question maybe through meeting requests. And so there is a commitment to publish a frequently asked question document that could be put out a little bit faster than traditional guidance with the hope that, that not only provides key information to sponsors of applications, but also create maybe a faster process to understand current thinking, perhaps in the future, maybe in a more iterative manner.

So, with that, I'm going to turn it over to my colleague Lucy for additional comments.

MS. VERESHCHANGA: Good morning, everyone. Lucy Vereshchanga, PhRMA. And I'll start with emphasizing the overall importance of PDUFA for biopharmaceutical innovation and for patients. So -- and we believe that PDUFA VII includes all this critical provisions that will advance innovations for patients.

And I wouldn't repeat all the great things that were just said about cell and gene therapy provisions, but I would just -- building on Cartier's

Page 25

comment, I'll just emphasize the importance of the patient centric approach to drug development, specifically for cell and gene therapies. And the importance of public process for gathering patient input for cell and gene therapists. We heard about dedicated meetings for patient-focused drug development disease areas, and also would echo what Cartier said about the importance of external collaborations.

It will help to advance thinking in using novel approaches and obtaining safety and efficacy information, for example, from real-world data evidence, nature history (ph) studies and other novel approaches. I'll stop here.

MR. THOMPSON: All right. Thank you both very much. We will now move forward with an overview of the proposed enhancements for Pre-market Review. And could we have the slides please.

Our FDA presented for this topic will be Peter Stein, our Industry speakers again, we'll be Lucy Cartier. After this session, we'll be taking a break. Peter, you have 25 minutes and you can start whenever you're ready.

Pre-Market Review Proposed Enhancements

Page 26

MR. STEIN: Great, Graham, thank you very much, and good morning, everybody. I served as the lead for the Pre-Market PDUFA VII review. And I will share with you some of the enhancements and new programs that I think will enhance the efficiency and provide areas for innovation in how we -- how we do pre-market review of drug applications.

I think you'll see that some of these programs really are geared to target areas -- of important growth areas like rare disease and real-world evidence that I think these programs will support and facilitate.

Next slide. So, what I'll do is, I'll walk through the programs that are part of the PDUFA VII commitment and talk about their role and importance. So, let me start with the enhancements for post-marketing requirements. Of course, when we complete a review and a drug has to be approved, there may still be some issues that require some additional clarification, additional data generation after approval, these are then -- can be put into post-marketing requirements.

Of course, the very detailed assessment plans are specified in a protocol that may be after approval, but the key elements -- the key design elements of the

Page 27

study or trial need to be in the post-marketing requirement at the time of approval. It's important to be able to provide this information in sufficient time prior to the approval action, so that there can be review and discussion and clarification of these PMRs. And so, what we've set up here is a new process to set up timelines to assure that the development of these PMRs are optimized, and there's sufficient time for appropriate clarification discussion.

So, in addition, we recognize that over time some PMRs may take a number of years to complete, the situation may change, scientific and clinical environment may have changed or evolved. And so, it is important that these PMRs be reviewed, and they can already be reviewed without this enhancement. But this allows for another level of review of the PMRs to determine whether they still are relevant and appropriate, or whether some change in the PMR or need for the PMR has changed. And of course, we will be updating our MAPPs and SOPs and guidances with these new timelines and processes.

Next slide. Another program, which I think is very exciting, and this comes out of a pilot program that had been ongoing -- that has been ongoing in the Office of Oncology Drugs, OOD, which is called -- which

Page 28

has been called the real-time oncology review. And out of that same -- out of that program, we've developed an applications that will be across divisions and offices, and this is called the split time -- Split Real-Time Application Review or STAR as the acronym.

The idea here -- the intent here is that for particular drugs, where there's a supplement that addresses a very important need in a serious disease, an unmet need that we would like to be able to enhance the efficiency of the review and bring the action earlier, so that the drug could be available, so this new indicated use can be available earlier for patients if it's appropriate to add this use to the label.

The idea here is that instead of the submission being entirely complete at the time that it's submitted, that this would allow for the majority of the information that we would get into submission to be -- to be president at the time of the initial component of this. But certain elements might be submitted a month or two months later.

And, in particular, the completed study reports and the integrated summaries can come in a little bit later, approximately two months later. But the initial submission includes all of the datasets, these protocols, and many, many other such elements

Page 29

that are essential for us to sort of kick off our review.

As you may know, we largely do take the datasets and we review both the efficacy and safety. We do our own analysis of all of these things. And so getting the datasets and protocols and statistical analysis plan really allows us to kick off our review earlier, and be able to do the analysis that are essential for us to be able to complete and determine whether the label update or a new indication is appropriate.

The goal here would be for us to be able to take action earlier, a month earlier, even two months earlier, based upon our ability to kick off the review earlier. So we think this is an innovative approach, and we'll be looking forward to seeing this coming to the fore.

And, obviously, we will be providing information in a public facing webpage, have a public workshop to discuss the program and our learnings from this, and the assessment of the effectiveness of this program, whether it achieves the goals or trying to move -- to move action dates earlier so that we can, you know, get drugs available to patients with these new indications earlier.

Page 30

Next slide, please. The next program I'm going to talk about is creation of two new meetings. As there has been obviously great new innovation in the areas of drug development, as sponsors look at new platforms for creating drugs or new targets, sometimes novel issues come up even before the program has gone too far before -- well, before it's gone into humans. And as early development is proceeding, issues may be -- need to be addressed that could use FDA input to facilitate development.

Typically, array these may be subject to what we've sometimes referred to as pre-IND meetings. But this program called INTERACT, sort of instantiates that in a more formalized way. The program really comes from a pilot program that's being -- as part of what -- that has been in CBER and this program allows us to be expanded. And again, the intent here is to set up meetings where a sponsor may have a very specific question typically that emerges from innovative programs, such as where there's a new platform, and allows us to have a discussion with the sponsor, give them earlier advice, and hopefully, therefore facilitate their development, which may otherwise be delayed.

Another meeting -- another new meeting is what

Page 31

we refer to as a Type D meeting, where we have what are called Type C meetings. These are meetings that can cover a wide range of different issues that occurred during development -- everything from issues relating to clinical trial or pharmacology information, toxicology, chemistry, manufacturing information, a wide range of different issues might come up.

And Type C meetings can often have a number of different issues that are pulled together by the sponsor to support a meeting between the sponsor and FDA to provide so that we can provide input on this range of issues.

Well, a Type D meeting is intended to be more focused where there might only be one or two issues that are narrower. And because it's a smaller number of issues, the timelines can be accelerated, which then of course, allows for more efficient development as FDA advice can be sought and provided earlier than -- in the Type C meeting format. So, we hope that this does facilitate development by giving feedback earlier.

In addition, what is not uncommon is that after there's a meeting, particularly where there are a number of issues, there may be areas that the sponsor wishes to get clarification, there may have been an agreement, but sponsor may want to make sure they

Page 32

understood it completely. And that they -- that they understood fully what the direction from the FDA was. And so, we've added a process by which meetings -- which questions which are really just clarifications of issues that came up at a prior meeting can be submitted and input given back in a timely fashion back to company.

We will have a public workshop about these meetings and appropriate training and of course, updated guidance, which will also include updated guidance on best practices in the management and communication to make sure that these important interactions are facilitated and as efficient as possible.

Next slide. I think as many are aware, we've seen a certainly a marked increase in the number of programs that are targeting rare diseases over the past decade or even more. One of the challenges in rare disease drug development is that for many rare diseases, where there still is a great need -- great unmet need for treatments, trials can be challenging. In particular, for example, the need to develop endpoints that reflect and can capture patient benefit from drug therapy may not yet be available, or well understood -- or the characteristics of these endpoints

Page 33

may not be very well understood.

So this is an exciting pilot program in which a sponsor, early in their development of a drug for rare disease, can come to us with a proposal for a novel approach at that point and it allows us to work closely with him on the development of that endpoint over a series of meetings.

The idea here is both to facilitate the development of an endpoint for a particular disease, but also to encourage innovation in how endpoints are crafted and created, and developed. Endpoints that we hope -- approaches to endpoints that we hope will be applicable not just to the particular rare disease for which that endpoint was developed, but for others similar rare diseases, capturing similar issues that may facilitate development across other rare diseases or even diseases that are not rare.

The intent here is to encourage this interaction between sponsor and FDA staff to enhance the development of these novel, innovative approaches to endpoints that facilitate the development of rare diseases as well as potentially in common diseases.

We will include multiple public workshops to talk about these strategies for endpoint development that we hope will then allow us to come up with

Page 34

principles and concepts and policy that may then be captured in guidances that then enhance the development of endpoints more generally.

Next slide, please. Another program to note is for what are called use related risk analysis as well as human factor validation studies. Before a human factor validation study, which addresses the use of combination products, drug device or biologic device combination products. Of course, a human factor validation study shows that the end user, whether a patient or healthcare practitioner, should appropriately use this combination device.

One determination as to whether a human factor validation study is actually needed is what's called the use-related risk analysis. It assesses the types of risks that might occur and determines whether those risks are sufficient to be -- that need to be addressed by such a study or might not need to be addressed by such a study.

We're seeing an increasing number of requests for review of these URRAs, and now we built a program with timelines and resources to be able to evaluate these use-related risk analysis in their appropriately timely fashion, which can then inform whether or not a human validation -- human factor validation study is

Page 35

needed, and as well as design elements related to that human factor validation study, so this should help in the timeline and timely development of these combination of products. A guidance that would be relevant to this, would also be -- would also be developed.

Next slide. I think another very exciting program is related to real-world evidence. Of course, this has been an area of great interest and importance over the past year's emerging PDUFA VI, and there's been a great deal of work in FDA, Industry and academics and other stakeholders on the use of real-world data and creating real-world evidence that can support -- potentially support regulatory decisions.

This area is certainly challenging. It's a novel approach to the use of real-world data. And there are many issues related to the types of data, sources of data, how the data is to be analyzed, comparison groups that emerge as we try to look at studies that utilize real-world data and create real-world evidence and are intended to support regulatory decision making. And so, these challenges have to be met. It require a lot of discussion between sponsors and FDA on the appropriateness of the study design, whether it's sufficient to be able to develop the data

Page 36

that we would need to support a regulatory decision.

So from those challenges, we've developed this real-world evidence program. And this pilot program basically seeks to have greater interactions between the sponsor and FDA. The idea here is that rather than get a finally developed study protocol forwarded to us, that we -- you would start sort of earlier, provide input to the -- to sponsors earlier. The idea would be that initially, we would have sort of a concept sheet proposal.

If this looks very promising then it really might ultimately be able to be developed into a study that that could be sufficient for supporting a regulatory decision. This would be then entered into this pilot program, and the program would include the opportunity for multiple interactions back and forth between the company and the FDA, sort of developing the stages -- through the stages of the development of the -- of this real-world evidence protocol.

The idea would be that each of the key components could be then discussed -- the source of data, the analysis approaches to the data, the development of control comparative groups, and the like could be discussed and the FDA feedback can be provided. So then ultimately the protocol that then

Page 37

would be implemented has a greater chance of developing data that is more as it could be potentially if -- depending upon how the data emerges, potentially could support a regulatory decision, and therefore, be able to support an expansion of label with new indication, new population of use.

So, this we hope will also provide broader lessons in how such robust studies could be -- study protocols can be developed. We'll be reporting the submissions on public facing annual report. And this also going to be a public workshop and meeting which will discuss the kinds of learnings from these cases, that could then provide more general and broader input as to how to craft the right kind of study that can have sufficient robustness to support important regulatory decisions.

And of course, the learnings from this, as we develop new policies and approaches, can be then crafted into guidances to reflect this experience from the pilot program. So, I think this is an exciting way of further utilizing real-world data, real-world evidence, and helping in working with sponsors to channel the interest in this towards what we hope will be studies that can ultimately be utilized to support regulatory decisions.

Page 38

Next slide, I think, that's a summary of the PDUFA VII program, so I'll turn it back to you, Graham.

MR. THOMPSON: Alrighty. So Cartier, and Lucy, you have five minutes, it's all yours.

MS. ESHAM: Sure. And thank you, Peter. That was a great summary. And, again, I'm just going to underscore a couple of things.

I would say that, you know, one of the sort of evergreen issues as we go into these PDUFA discussions is really, how can we ensure that we are setting up processes and a system that enable scientific dialogue throughout the development and review cycles to best ensure that we are able -- setting up a system that enables us to do early issue identification, and early issue resolution wherever possible. And I think the outcome of this agreement is very exciting in that aspect.

As Peter outlined, there is the new -- there's an expansion of the INTERACT program that was very successful at CBER that's not going to be available for products undergoing review at CDER. It establishes timelines for both, so that the expectations of how to prepare and be prepared for those meetings, as well establish and supported by appropriate resources.

The ability to have the new Type D meeting to

Page 39

have focused conversation. So, I think this is of particular import when you have a particular challenging issue, or a novel issue where you want the ability to have a focused discussion, is a very exciting new offering in this PDUFA agreement.

The ability to have a prioritization for sponsors' requests where there is very little precedent known or there's a really -- it's a very novel program, the ability to at least have -- if you received a written only response to have a prioritization of a sponsors' request to convert that to a face-to-face. Again, there is a very nice offering in this PDUFA agreement. Again, all of these meetings are both for CBER and CDER.

And Peter mentioned the follow-up meetings. And again, this is an issue that's been discussed over the years, and I think that this is a very nice process -- a newly established process to really enable a quicker -- a quicker timeline to do this simple and clarifying questions to make sure you heard what you heard, and to verify that before you -- perhaps you're going to go off in a wrong direction. And again, that's just going to create efficiencies in the process, both for FDA and for biopharmaceutical sponsors.

Page 40

The other thing that that Peter mentioned, but again, I'm just going to underscore for the audience today is, that there will be public meetings and updated guidance on meeting management and meeting practices. And what I want to underscore there is this is the ability for industry to also learn about are we ensuring that we are best preparing ourselves for the most productive meetings, and that's really important. That will be a very important engagement and understanding to be gained through the commitments in this PDUFA letter.

Peter also mentioned the new processes to ensure that for any post-market requirements that a product may have, that the engagements happening during the review cycle are done in a manner to best ensure agreement on a solid study plan. So, a solid approach to achieving those post-market requirements once -- prior to approval. And then the ability of science evolves or thinking evolves to go back and a process to have the study requirements reviewed by the Agency, whenever appropriate.

And we're also very excited, and again, I think it's always good when you see a program -- the STAR pilot program, which is modeled after something we saw very beneficial in the oncology space, the RTOR

Page 41

program. And to be very clear, this is not in replacement of RTOR, it is in addition to. So, it is a pilot program for efficacy supplements across FDA to really -- but take what we saw worked very well in the oncology space and apply it in a pilot program to efficacy supplements to gain learnings about how that sort of two parts submission may enable more efficient and effective review.

So again, that's something that's very exciting, and I think it's always good to have pilot programs that are expanding on areas that we saw work very well. So, we're very excited to see that get started and look forward to the learnings that we obtained from it.

With that I'm going to turn to my colleague Lucy.

MS. VERESHCHANGA: Thank you, Cartier. And I would like to emphasize Peter's comments on the increased use of real-world evidence.

So, the PDUFA VII provisions will build on successes that were started in PDUFA VI, also builds on some of the 21st Century Cures milestones. And as Peter mentioned, there been quite a few stakeholder discussions and efforts over the past 5 plus years. So we're really looking forward to successfully building

Page 42

on all those efforts. So, this is why industry supports a pilot program for real-world evidence.

And importantly, the pilot will include an increased public transparency element. So, as Peter mentioned, all the learnings coming out will have to be publicly posted, there are multiple stakeholder workshops attached, and opportunity for stakeholders to provide input and really have meaningful discussions -- how to increase regulatory acceptance of real-world evidence. And that arguably can be used not just for safety purposes, but also can support efficacy indications.

So, I would also emphasize previous provisions for rare diseases. And industry and FDA, definitely want to continue to ensure robust support for rare disease drug development. And specifically PDUFA VII establishes Rare Disease Endpoint Advancement Program. And it will help sponsors to understand better how to engage with the regulators on developing endpoints, specifically for rare diseases. I'll stop here.

MR. THOMPSON: Okay. Thank you everyone so far. We're a little ahead of schedule, but I think we're going to move into taking a break anyway.

And we're in the next slide, I know the slide says 10:25, but I ask everyone to be back at 10:15 and

Page 43

we can send out a notification in the chat as well. I will come back then.

And while everyone's on break, just another plug for the public docket, if you want to submit written comments. With that, we'll see everyone back here at 10:15.

(Recess)

Regulatory Decision Tools Proposed Enhancements

MR. THOMPSON: The next session, which is regulatory decision tools, to get ready. That's you, Theresa. And we'll begin in just about half a minute.

All right. Thank you. And if you could advance to the next slide. Okay.

So, we're going to move on to our overview of post-enhancements on regulatory decision tools. Our presenter will be Theresa Mullin, and our speaker as usual will be Lucy and Cartier. And Theresa, you can start whenever you're ready.

MS. MULLIN: Okay. Thank you, Graham. Hello, everybody. Good morning. I'm Theresa Mullin. And it's my pleasure to take you through this section of the enhancements proposed for PDUFA VII.

And I'm going to be focusing on three

Page 44

enhancements and these are in that section of the commitment letter, if you'd taken a look at it. And one is patient-focused drug development, another model-informed drug development. And the third, complex innovative trial designs.

And these are -- essentially these were the three that were under active discussions with industry in the past year. And these are the ones where we had some evolution of the commitment and what's involved in this program.

And so, if we can go to the next slide, please. And I'm going to just give you a little background, because these three are in fact continuations and extensions of the work that was continuing from work done under PDUFA VI, and in some cases even before that. A little bit of background before we get into the proposed enhancement.

And so, the first one, patient-focused drug development. Here we're -- our goal is to advance the patient's voice in drug development and decision-making. And what we recognize is that patient input, if it's collected in ways that are methodologically sound, and produce valid and reliable sort of assessments and endpoints that can be used, this can provide evidence for regulatory decision-making.

Page 45

And similarly, patient preference information can help inform regulatory decision-making if it's collected in a way that's methodologically sound. And what we find is that studies may have quality problems. And so, they may not be as useful as we ideally would like them to be. The information that's collected is not as useful in decision-making. And so, that's not the best use of the time, an investment of patient's time and resources expended to collect this information.

And so, in PDUFA VI we've been developing a series of methodological guidance, focused on clinical outcome assessments or COAs. And those are still under development now. And we, you know, expect to have those finished before the end of this current authorization cycle. But the enhancements for the coming period are really building on that.

And so, they include expanding training both to prompt internally focus training on new divisions and stakeholders within CDER and CBER with an emphasis on those methods and tools. And also, a train -- focused training and outreach to industry and other users of this mythological guidances so that they have a good -- they know they're there, their awareness, understanding of them, and that they're making maximum

Page 46

use in order to have high quality evidence being submitted to FDA.

In addition to that, we'll be issuing a request for information to collect input from stakeholders to understand what the methodological challenges are, and what needs to be further discussed. And that will form a basis of planning agendas from two workshops that would be held during PDUFA VII, to really explore those methodological issues.

Another component of this commitment refers to the virtual catalog of standard core PDUFA outcome assessment measures that FDA has been developing using the budget authority funds that we received through Cures that were initially authorized under Cures and have been appropriated by Congress under the Cures Act, or following what was described in the Cures Act, but in our annual appropriations.

And these non-fee funds are -- would continue to be used and would -- we would not be using these (inaudible) funding for this. But there's a reference to this work in the commitment letter with the idea that this is an important component of patient-focused drug development. And what we would be doing is seeking additional stakeholder input about priority disease areas and domains that would be of interest to

Page 47

be included in this virtual catalog.

And the last thing that I'll mention with patient-focused drug development is that there's a piece in there for developing a future guidance on patient preference. And this would be development in 2026 time frame, and that's another addition to enhance the quality of the kinds of submissions we been receiving for patient-focused drug development.

So, next slide, please. Another enhancement is focused on model-informed drug development, MIDD. And MIDD can really improve the efficiency of trial designs and reduce uncertainties and help actually developers and the agency explore those uncertainties to find out which matter and how to better design our drug development programs.

And it's -- we've had a pilot in PDUFA VI with a paired meeting involved, consult with companies or companies coming to consult with FDA about their plans and how they are using these models. That pilot is very successful, and so the goal here under PDUFA VII is to continue and turn that pilot into a formal program, continuing program. It's no longer a pilot. But keep it within that same footprint that was established under PDUFA VI.

And so, what is involved is the agency being

Page 48

willing to accept up to eight proposals per year, one to two per quarter is the, you know, the cadence at which things would be expected. And these basically would involve a pair of meetings that are focused on the same drug development issues.

And the second meeting in this case would occur approximately 60 days after receiving the briefing materials that, you know, following that first meeting. And the discussion would be on those (inaudible) program issues if there -- a sponsor wants to have this kind of consultation with agency and the eight programs have already been taken up for a given year, they can still come into the normal and other traditional meetings options that are available to sponsors.

In addition, there will be a request for information the FDA would issue to understand what areas of development or MIDD work would be of greatest priority to outside stakeholders for future guidance development.

Next slide, please. And this is the third one, the final one that I'll talk about today. And it's on complex innovative trial designs. Now, we had a pilot for this as well in PDUFA VI, and it was similar in the sense of a paired meeting approach. And

Page 49

this is really focused on a wide range of indications. Really many different designs had come in through this program.

And they all involve this computational intense analytic techniques and situations that had to be used, a lot of time interaction is necessary to make this really worthwhile between FDA and the sponsors. And we find that in addition to the later-stage development, they're increasingly -- these kinds of designs are being used in earlier phases of drug development.

And so here, the enhancement that's been committed to is that again will be transfer – translate or rather transitioning from a pilot to a full-grown program here with the goal that this would continue to advance and facilitate the use of adaptive designs and it would be easier designs.

And, again, it's a pilot program -- a paired meeting program. And in this case the second meeting would be approximately 90 days after receiving the materials following that first meeting. There would be one to two per quarter accepted by CDER and CBER together, that's the total for FDA, up to eight per year.

And in addition to that, the other components

Page 50

of enhancement here are that the whole goal here is to have not just this individual sponsor who is submitting this innovative design be gaining that experience and knowledge but to have others as well. So, a piece of this pilot program is that the trial designs developed through paired meeting program may be presented by FDA as case studies, including the drug that was studied and may not have been approved yet by FDA. That's one of the understandings from people entering this program. It's not a pilot anymore. Sorry.

And there -- when FDA discusses a company joining this program, there is an understanding and discussion of the information that FDA plans to share in those case studies. And when feasible, FDA would notify the sponsor in advance of sharing that information publicly.

Sponsors who don't participate in the paired meeting program again have an opportunity to come in through other meeting, traditional meeting channels. And there will be a public workshop that the agency plans to have to discuss various aspects of complex designs, basic designs and other novel designs, and that would be in the 2024 timeframe.

And finally, there is a commitment to issue a draft guidance on use of methodologic -- use of phasing

Page 51

methodology in critical trials for drugs and biologics. And that is aimed for in the 2025 time period.

And with that -- those are the new enhancements for regulatory tools in PDUFA VII. And so, with that I'll close.

MR. THOMPSON: All right. Can we do the next slide. We'll move on to Cartier and Lucy. Thank you.

MS. ESHAM: Thank you, Theresa, for that excellent summary. And I'll just again provide a few color commentary. Think this really -- has really been an evolution going back to PDUFA V, and it's a continuation of that journey that started significantly in PDUFA V where there was a commitment in the PDUFA V agreement to have post a series of Voice of the Patient meetings which were extraordinarily enlightening where we as a community really learned not only the importance but how to think about what matters to patients and how to think about capturing patient experience data.

That led to the PDUFA VI agreement where the goal there was to really think about what is needed, what do we -- what resources do we need to provide the FDA to sort of collectively advance a systematic integration of patient experience data into drug development and review processes. And that resulted in

Page 52

a significant amount of resources being provided under the PDUFA VI agreement, I believe over 60 FTEs, I believe 63 FTEs were provided under the PDUFA VI agreement.

So as we going to PDUFA VII, what we wanted to do is to make sure that those resources provided under PDUFA VI are maintained and continue that very important work of focusing on patient-focused drug development. And we wanted to expand some resources to continue to advance our thinking. So, I think in terms of the patient-focused drug development, we're very excited about the commitment of relating to the ability to have some workshops, the ability for community to have public input, to continue to advance our thinking and our shared understanding about how to submit and evaluate patient perspective data to support benefit, risk evaluations and to support labeling activities.

We're also -- we are very supportive of the continued development of the virtual catalog that -- on standard core sets of clinical outcome assessments that Theresa mentioned, and we look forward to continuing to provide input to continue to strengthen that catalog.

And lastly, I'll just underscore, we're also very excited about the commitment to have draft guidance on the use of patient preference studies. So,

Page 53

again, this marks sort of a continued evaluation of our shared understanding and shared thinking and advancement of how we are collecting patient perspective data, how that can be utilized for specific regulatory decision-making, to ensure that the voice of the patient is in fact becoming integrated into how we approach development and review of drugs and biologics.

With that, I'll turn to my colleague, Lucy.

MS. VERESHCHAGINA: Thanks, Cartier. And to echo Theresa and Cartier, complex innovative trial designs and model-informed drug development is another example how PDUFA VII builds on successes from the previous cycles, specifically PDUFA VI, and will continue to advance innovative drug development and regulatory decision tools to the benefit of patients.

And I would like to specifically emphasize public process and public workshops series on novel, complex, adaptive and Bayesian designs, that they will issue guidance on Bayesian approaches. So the work will continue and build on the efforts from PDUFA VI.

PDUFA VII also continues model-informed drug development, pair missing programs, as Theresa mentioned, and importantly will be enhanced by issuance of request of information to elicit stakeholder input for identifying focus areas for future policy or

Page 54

guidance development. So, we look forward to this enhanced stakeholder engagement. And as Cartier said, we're very excited about these continuing efforts.

MR. THOMPSON: Okay. Thank you very much.

Post-Market Safety Proposed Enhancements

MR. THOMPSON: We're going to move on now to our fourth session on Post-Market Safety. Our FDA presenter for this topic is going to be Terry Toigo and same industry speaker as always. Terry, you're up next, and you can begin whenever you're ready.

MS. TOIGO: Okay. Thanks, Graham. As Janet Woodcock mentioned before the technical issue started with the -- her presentation, drug safety is a critical part of FDA's public health mission. As Andy mentioned on -- in PDUFA IV, drug safety was added to the commitment.

And since then we've continued to use the user fees to enhance the drug safety system. Our goal remains to improve public health by increasing patient protection while continuing to enable access to needed medical products for patients. So, I'm going to, in the next four slides, I'll walk through our commitments related to REMS and Sentinels, which are part of PDUFA

Page 55

VII.

Next slide, please. So, as part of the reauthorization of PDUFA V in 2012, FDA committed to standardize and assess the effectiveness of REMS and to better integrate them into our healthcare system. These activities included two guidances that were published in January of 2019. The guidance did help advance the science of REMS program assessment and helped sponsors develop the REMS assessment plan.

But a remaining area of concern is to complete timely assessments, and for us to be able to determine whether REMS is doing a good job of meeting its goals and ensuring that the benefits of a particular product outweigh its risks and whether FDA should take action when -- when a REMS is not performing as expected.

So, although there were not any specific REMS commitments in PDUFA VI, FDA did continue its REMS standardization effort. PDUFA VII commitments established, as you can see on this slide, established FDA review performance goals for -- after reviewing REMS methodological approaches and study protocol for REMS assessment.

Also included is an FDA commitment to develop and incorporate REMS assessment planning into the design of REMS to help identify key metrics for

Page 56

success. This will also help us ensure that sufficient data collection is built into the design of REMS for determining whether or not a REMS is meeting its goal.

We'll meet this commitment by creating new guidances or updating existing guidances or policies and procedures to determine whether modifications to the REMS or revisions to the REMS, assessment plan are needed, and whether that REMS is still necessary to ensure whether the benefits of the drug outweigh its risks.

We believe that the PDUFA VII REMS assessment, REMS commitment package will enhance FDA's ability to determine whether or not REMS are meeting their goal.

The next three slides, if you could move to the next one, address commitments to optimize the Sentinel Initiative. In the last 5 years, the Sentinel Initiative, which includes both the Sentinel System and BEST, or the Biologics Effectiveness and Safety System, has become an integral component of FDA's routine regulatory review program. With operational processes and policies and ongoing scientific training programs and clear evidence of regulatory impact. Sentinel analyses have influenced dozens of regulatory determinations, including labeling changes and presentations to advisory committees.

Page 57

This work has in many cases enabled FDA to resolve safety concerns in-house and then thus prevented FDA from sending additional information requests to companies or in some cases requiring post-marking studies. FDA is implementing several enhancements, including new data linkages and data sources like Medicare data in these Sentinel centers, both of which help improve Sentinel's capability.

The growing complexity and then the sophistication of the Sentinel Initiative has introduced a different set of challenges and heightened our resource considerations. And, as you can see from the bullets on the slide, the commitment will provide continued support to help FDA sustain a strong post-market population-based surveillance capacity, will meet these commitments by maintaining the quality and the quantity of data available through the Sentinel Initiative, and processes and tools for determining how and when the data are utilized. Engaging in staff training, communicating with sponsors and the public through dissemination of scientific advances at public meetings and public training.

Next slide, all right. Additional resources, as described in this slide and the next one, will enable FDA to focus on improvements to Sentinel areas

Page 58

efficiency and BEST on product safety by initiating scientific development projects in Sentinel and BEST around areas of insufficiencies that are of mutual importance to -- with industry and that's product safety and pregnancy and negative controls, which I'll discuss in the next slide.

But, monitoring of safety of it's -- of the safety of its regulated products is a major part of FDA's mission to protect public health. Because pregnant women have historically been excluded from drug development trials, there's often limited or no human data to inform the safety of use of the drugs in pregnancy and labeling at the time drugs are approved.

The goal of the pregnancy safety post-marketing and PMRs and PMC studies is to inform labeling on the safety of use and pregnancy and to detect or evaluate safety signals in a timely manner.

So, the first of our new commitments to optimize the Sentinel Initiative includes supports for the development of a consistent approach for assessing the outcomes of pregnancies in women exposed to drugs and biologic products. We plan to develop a framework for how data from different types of post-approval safety studies, pregnancy safety studies have been used by FDA, and to identify gaps in knowledge that need --

Page 59

that will need to be filled by demonstration projects.

We'll then hold a public workshop on post-approval safety studies in pregnant women, to facilitate the determination of optimal post-market study design, which could include Sentinel resources from the Sentinel Initiative. And then using the feedback from the initial framework and the workshop, we'll conduct five demonstration projects to address gaps in knowledge about performance characteristics of different study designs in the context of the proposed framework developed.

And then finally, we'll update the proposed framework with the results of the demonstration projects to develop a guidance or a MAPP to implement a standardize process for determining the necessity and the type of pregnancy PMRs or other post-market studies or activities.

Next slide. The second new commitment to further optimize the Sentinel Initiative involves development of new methods to support causal inference for product safety questions, that will also help our -- advance our understanding of how real-world data may be used for studying product effectiveness questions.

FDA is building BEST in Sentinel methodology to improved our understanding of how negative controls

Page 60

can be used in robustness evaluation to address the consistency of real-world evidence with respect to study design analysis or variable measurements. And as listed on this slide, the commitment also involves a public workshop and two methods development projects. And the deliverable for this commitment is a final report that is due at the end of PDUFA VII.

And -- so, in the area of post-market safety, I think as these commitments demonstrate, FDA will continue to use user fees to enhance the drug safety system through modernization and improvement of REMS assessment and optimization of the Sentinel Initiative.

And by doing so, we will continue to improve public health by increasing patient protection while continuing to enable access to needed medical products. So with that, that ends the discussion on the post-market safety commitments. And I will turn it back to Graham. Thank you.

MR. THOMPSON: I'll take that and turn it over to Cartier and Lucy for the industry perspective. And thank you very much Terry.

MS. ESHAM: Yes, thank you, Terry. And, again I will concur with the absolute import of the ability of the FDA to maintain a quality safety system. And this is reflected in the historic and continued

Page 61

significant commitments and resources provided under the PDUFA agreement.

I will also, you know, I think, I will underscore the commitment to have the publication of information to improve communication with sponsors and the public regarding general methodologies for Sentinel enquiries we think will be of high value. And additionally, really thinking about not just maintaining the current role of the Sentinel initiative but evaluating the possibilities of use of data such as real-world evidence that could be utilized for other purposes such as regulatory changes for post-market requirements or commitments, labeling changes, et cetera, really continues to advance the value of the Sentinel Initiative.

With that, I'll turn it over to my colleague, Lucy.

MS. VERESHCHAGINA: Thanks, Cartier. I would emphasize FDA's and industry commitment to patient safety. And also as Cartier mentioned, we try to take a holistic approach to how we view PDUFA VII provisions and make sure that to the extent possible will leverage the ongoing effort, continue building on that and put enhancements in place, specifically as Cartier mentioned on increased use of real-world evidence and

Page 62

how we can advance Sentinel analytical capabilities to support the use of Sentinel, to address product safety and also to address how real-world evidence can be used for demonstrating drug effectiveness.

I would also emphasize that PDUFA VII includes important initiatives related to safety of pregnant populations. And a specific example there is public workshop on post-market safety studies in pregnant women to facilitate determination of appropriate post-market study designs. And it would include industry experiences on how Sentinel and other real-world data resource can be used for these purposes. And would like to also echo the importance of the new Sentinel demonstration project for specifically addressing the pregnancy outcomes in women and really the support that PDUFA VII will provide for implementation of a standardized process for determining necessity and type of pregnancy post-marketing studies.

So, I'll stop here.

MR. THOMPSON: Okay. Thank you, everyone.

MR. THOMPSON: We're going to move into our next session which is on Chemistry, Manufacturing and Controls. Our FDA presenter for this topic will Carol Rehkopf. And you can begin whenever you are ready.

Page 63

Chemistry, Manufacturing, and Controls Proposed Enhancements

MS. REHKOPF: Very good. Thank you so much. As mentioned, my name is Carol Rehkopf. I was one of the negotiators during this PDUFA cycle. And the same subgroup was one that I supported. And it's a real pleasure to be with you today. Next slide, please.

So, as Andy mentioned at the start of this meeting, this section is really a new commitment. The CMC section comes through manufacturing and controls. This new topic is an opportunity really for us to enhance our communications in this space and to also advance the use of innovative manufacturing technologies. And what I'm going to do today is really summarize the various commitments. And I encourage you to read the commitment letter itself to understand the details more fully.

So, in this effort to enhance communications, including providing structured CMC information requests and communication at appropriate time points within the review cycle of the product lifecycle -- I'm sorry, of the product life cycle. We refer to the structure communication as Four-Part Harmony.

Page 64

So, Four-Part Harmony is something that we committed to, and it includes acknowledging what was provided in an application and where, identifying the issues and efficiencies that we've -- that we have identified in clearly explaining that information. And also information that's need to achieve resolution of any issues or deficiencies that were identified. All of this is in an effort to help us get to a regulatory decision.

So, FDA is committed to updating procedures and providing training on the four central components of Four-Part Harmony. These include describing what was in the application, a description of those issues and deficiencies, what's needed to -- for FDA to understand the issue better or to address the deficiency and an explanation of why it's needed.

To assure good FDA communication, training will be updated on the CMC assessment process as well. And this is related to the mid-cycle and late-cycle review meetings that we have. The goal really is to ensure that the mid-cycle and late-cycle meeting expectations are met. This also includes the status of the NDA or BLA CMC assessment, and making sure that's communicated well, in addition to any issues that have been identified that would preclude approval.

Page 65

We have committed to a third-party assessment on sponsoring FDA communication practices through product quality information request. And so that's something that we planned to perform. We really want to focus on the area of assessments and the application of Four-Part Harmony and how well we're doing in the space. We want to identify trends across information requests as well.

Both FDA and industry believe that enhanced communication between review teams and industry on inspection-related activities are important. Therefore, for applications, not including supplements, where FDA feels that the manufacturing process must be observed, the FDAs agreed to the goal of notifying a company about those pre-license or pre-approval inspections at least 60 days in advance or no later than the mid-cycle meeting when facilities need to be inspected in those cases. So, again, this is when manufacturing is in process. This will help to ensure that FDA can observe operations during an inspection and will help facilities plan accordingly.

Next side, please. Thank you. So, during the COVID-19 public health emergency, travel essentially stopped. And therefore we had to think of other ways to assess manufacturing facilities when it was

Page 66

feasible. Because of this, FDA expanded its use of alternative tools for assessing facilities named in applications, including exercising its authority to request records and other information in advance of or in lieu of an inspection.

So, where appropriate, the agency increased the use of that available information, including inspection reports shared by trusted foreign regulatory partners we have around the world, through mutual recognition agreements and other confidentiality agreements. These are areas where FDA continues to learn and understand what is possible. Given this experience, FDA has agreed to issue a guidance document on the current thinking and best practices related to the use of those alternative tools to assess manufacturing facilities that are named in pending applications moving beyond the pandemic.

Again, those examples include things like alternative tools as in inspection reports from those trusted regulatory partners across the globe and also things like record requests or requests for other information from applicants or facilities and the use of new technologies as a possibility as well.

Next slide, please. Development programs for CDER- and CBER-regulated drugs and biologics intended

Page 67

to, you know, help the serious diseases that were contemplating and to meet unmet medical needs, we often have to think about accelerated clinical development timelines. So, products with accelerated clinical development activities face challenges oftentimes when it comes to CMC development.

We really are looking to have the CMC development activities align with that accelerated clinical development and those clinical timelines.

Overcoming these CMC challenges for aligning these activities requires additional interaction with FDA oftentimes, so that during the product development itself the use of science and risk-based approaches can be employed so that the clinical benefits of earlier patient access to these products can be realized.

So, in the spirit of advancing the use of innovative manufacturing technologies, a new pilot program called the CMC Development and Readiness Pilot or CDRP will be used in an attempt to expedite the CMC development of IND products are expected to have this clinical benefit for earlier patient access.

Sometimes accelerated clinical development occurs faster than the CMC development. We know this, right? So, the goal of the pilot is to achieve increased CMC readiness for those CBER- and CDER-

Page 68

regulated products.

So, what we intend to do is starting or -- is to start this in fiscal year 2023. And the commitment includes issuance of new procedure on approaches to address CMC challenges for CDER-regulated products with accelerated clinical development timelines and will include things such as early engagement with sponsors in different science and risk-based approaches.

The MAPP will incorporate modern pharmaceutical principles and modern regulatory tools such as those detailed in ICH Q12. Specifically, for sponsors participating in the CMC development and readiness pilot, FDA will provide specific CMC advice during product development, by providing two additional CMC-focus Type B meetings and an additional limited number of CMC-focused discussions based on readiness and define CMC milestones.

This increased communication between FDA review staff and the applicant is intended to ensure that there is a mutual understanding of what activities must be completed and what information should be provided at the appropriate time points.

These time points include things that are required in a NDA and BLA submission prior to the end of a review cycle or post-approval for example. All of

Page 69

this is really meant to ensure that the CMC readiness of the product is in place.

Next slide, please. A public workshop is planned where we intend to talk about CMC aspects of expedited development, and will include case studies, lessons learned, barriers to the adoption of manufacturing technologies, regulatory strategies for the adoption of advanced manufacturing, including submission strategies for implementation of certain innovative technologies across multiple commercial products and multiple manufacturing sites.

Stakeholder input about the pilot will also be solicited. And the topics of the workshop will include the best practices and lessons learned from the pilot, things from the CDER Emerging Technology Team and the CBER Advanced Technology Team programs from both the industry and regulatory perspectives.

I mentioned case studies from previous innovative technology submissions will be presented. And barriers, what are the technical and regulatory barriers to the adoption of innovative manufacturing technologies.

Regulatory strategies for the adoptions of advancements of these technologies will be included. And it will include things like submission strategies

Page 70

for the implementation of certain innovative technologies across, like I said, the multiple commercial products or multiple manufacturing sites, and that science of risk-based approach.

A draft strategy documents will be issued in 2024 that will outline the specific action that the agency will take after this workshop. The actions described will be based on the lessons learned and from the agency experience with submissions involving the advanced manufacturing technologies that we're talking about. It will also include feedback from the workshop itself. And it will be available for public input.

The strategy document may include updating or creating new procedures MAPPs, SOPs, guidances, and scientific or other relevant programs related to the topics discussed in the workshop. The strategy document will also include proposed timelines for specific actions outlined in the document. And FDA, as I said, will consider public input and finalize the strategy document within certain period of time.

So, to close, what I'd like to say is that we hope that these commitments in this new section will result in enhanced communications and the advancement of and the use of innovative and manufacturing technologies.

Page 71

With that, I'll turn it over to Graham. Thank you.

MR. THOMPSON: And, again, I'll turn it over to Lucy and Cartier. Thank you so much everyone.

MS. ESHAM: Thank you. Thank you, Carol, and hopefully it is apparent. There was a significant and appropriate amount of focus on this very important topic that was relatively new to the PDUFA negotiations.

And the reason for this was, from the -- by a pharmaceutical perspective, there was a growing sense of import and almost urgency about wanting to ensure that we were aligning on an effective process for CMC engagement, both to ensure that meetings were happening at the necessary times both in development and review, and that the meetings held were productive and effective for all sides, for both the regulator and the industry.

And so, there again I think -- I think there's a very positive -- many positive outcomes. And I'll underscore a few. The work that will be done to sort of promote the training, the third-party assessment to really promote a more structured CMC information request process we think is going to be of high value.

The pilot program that Carol mentioned, well,

Page 72

a pilot program may, to some, seem limiting, it is very much modeled after what we view as a very successful approach to the innovative clinical trial design, a pilot program that Theresa mentioned as part of her presentation. And that is -- while it is a pilot, the pilot will produce those extra engagements on -- to focus discussions on readiness and define CMC milestones.

But what will be of important to everyone is it does provide that sort of ability to share those learnings through case studies, through workshops that will result in a strategy document that will be published prior to the end of the next PDUFA cycle that will really, hopefully better advance us towards that ultimate goal of having, ensuring that these conversations are happening at the right time, and that those meetings are effective and productive.

So, far apart, again there was a lot of work that went into those. I think that I'm just underscoring a couple of things that we think are going to be of significant benefit. Lucy?

MS. VERESHCHAGINA: Thanks, Cartier. And I would like to echo industry's excitement on the, explicitly including manufacturing provisions and PDUFA VII performance goals (inaudible) and would like

Page 73

emphasize that industry and FDA consider and discuss the emerging lessons we learned from the COVID-19 pandemic response. And this is why PDUFA VII will include a draft guidance on the use of alternative tools to assess manufacturing facilities named in pending applications and how to utilized new or existing technology platforms as appropriate.

I also would like to emphasize what Carol said, that in advance of issuing this draft guidance, FDA will hold a public workshop. So, it's again opportunity for all stakeholders to provide input, how to advance utilization and implementation of innovative manufacturing technologies. And then, as Carol mentioned, FDA will issue a draft strategy document that will outline the specific actions that the agency will take. So, again, we're excited about these new provisions in PDUFA VII.

MR. THOMPSON: Okay. Thanks so much everyone.

MR. THOMPSON: We're now going to be moving into session six here, which is our Digital Health and Informatics review. And our FDA presenter for this topic is Mary Ann Slack. And Mary Ann, you can begin whenever you are ready.

Page 74

Digital Health and Informatics Proposed Enhancements

MS. SLACK: Thank you. Sound check. Graham, you can hear me well?

MR. THOMPSON: Can hear you loud and clear.

MS. SLACK: Okay. Wonderful. Well, let me apologize if my voice gets scratchy. The allergies have got me by the throat today. If you could go on to the next slide, we'll get right in to it. Next slide, please. Thank you.

Okay. So we'll start with commitment to expand capacity in digital health technologies. And I know that everybody here is familiar with digital health technologies and their impact on healthcare.

They hold a lot of promise in healthcare, and also in drug development, drug biologic medicinal product development. The use of these DHTs can support and enable a conduct of decentralized clinical trials, either fully and hybrid, and parts of traditional clinical trials. They allow collection of data in the trial participants' day-to-day environment, it can support safety monitoring without requiring frequent visits to a traditional investigational site, et cetera.

But CDER and CBER actually have limited

Page 75

experience. And we don't have enough expertise in evaluating DHT-generated data yet. We are getting DHT-based submissions and they've been steadily increased and then they're not going to go away. But the successful implementation of these DHTs in clinical trials depends on both sponsors and FDA being able to carefully assess the performance for their intended use and developing our capacity and expertise in that area, enhancing knowledge and capabilities in the areas of clinical outcome assessment, data standards, data management, et cetera. We need to build that capacity.

So, if you look at this commitment, you can see that it's recognizing both the potential and the challenges that the use of DHTs bring. And it helps FDA to meet those challenges and facilitate the effective use and review of DHT-generated data in new medicinal products development.

For instance, it increases FDA's capacity and expertise to advise the pharmaceutical industry in development and implementation of DHTs and how to evaluate those outputs. In addition to expanding capacity in this area, FDA is committed to holding a series of public meetings and workshops, conducting issued-focused demonstration projects, and issuing new or updated guidances as the need dictates.

Page 76

So, moving forward through with PDUFA VII, we'll be creating a DHT framework document to guide the use of the DHT-derived data in regulatory decision-making, and we'll be putting in place a committee, a cross-organizational committee to support that implementation, particularly collaborating with the recently launched digital health center of excellence an this framework is established and implemented. If we could -- excuse me.

So, some of the benefits of this commitment obviously increase our ability and regulatory acceptance, because we actually have that review expertise and capabilities. We can provide more clarity through guidances on expectations for sponsors developing these novel DHTs. It has the potential to enhance the inclusion of patient populations in clinical trials, enhancing review consistency, supporting communication, consistent communication and so forth, a myriad of other things.

And now I'll move on to the next slide. I'm conscious of time. Next slide, please. Oh, I'm so sorry. You have it up there.

So, this contains a lot of information on this slide. And you'll see there are connected but different commitments on here or agreements on here.

Page 77

The upside is that although FDA has long been accepting regulatory submissions electronically, we still have a lot of process and system inefficiencies, including the ability to automatically accept, validate and processing very large datasets, to be able to use modern technologies, cloud, for instance, cloud technology to extract and manage important information and execute resource-intensive algorithms on this. And we have made progress and we're still continuing to make progress, but there's a lot of opportunity out there.

So for instance, you have all seen, I'm sure. And if you haven't, please go out and take a look at FDA's Technology Modernization Action Plan, and the Data Modernization Action Plan, because they speak about key initiatives, key priorities that we're moving forward with and that this commitment helps to support. One is, cloud-forward, making it easy and agile to embrace the cloud, to use package services, and an agile and secure network architecture. Data center consolidation, for instance, for more streamlined operation. A modernized data environment.

The DMAP itself proposes a framework to drive the data strategy for deploying new systems that will allow FDA to manage and analyze data more effectively,

Page 78

more efficiently.
The cloud environment. Some of the challenges that we have right now with the cloud posture, cloud-forward posture, we still have challenges, we have difficulty to receive and process complex applications, especially those applications that are having, using very large datasets, because it's difficult for us to receive them directly electronically. It's tough sometimes to readily extract triage and streamline submitted data because of the way it comes in. There is opportunity for improved, more streamlined communications between FDA and sponsors.
Our current environment doesn't support sharing content or efficient content submissions to multiple regulators. For instance, if you think about Project Orbis with the Oncology Centre of Excellence, we have limited support for sponsored regulator collaborations in exchange, for instance, information requests.
So, looking at this, looking at this commitment, this agreement, you can see that there are multiple things that are listed here that address that. One is the resources to monitor and modernize the electronic submissions gateway and shift it to a cloud-based operation, to introduce the idea of these

Page 79

demonstration projects that would explore not just taking the standard operations and moving it to a cloud-based environment, but to promote innovation, what could be done, how could we modernize our regulatory review submissions activities, what could be done in terms of secure collaboration spaces.
We also are looking at doing all of it to further the TMAP and the DMAP. And we're looking to do all of this through this first commitment, which is to further enhance transparent environment of our activities and our modernization plans, leveraging these regular meetings between FDA and industry, IT leadership, and providing and monitoring update plans and updates against those plans and discussing reflecting on where the plan might need to shift because something is changing over the, you know, externally, over the course of time. And to be doing the same on other PDUFA-relevant initiatives.
Now, likewise, CBER is in a unique position. They need modernization of their critical IT. And this is not to imply that CBER stands alone and they'll have a parallel environment because that's not the case. But where they find themselves right now, as you heard earlier from Chris, in a situation where the volume and the complexity of biologic submissions, like cell and

Page 80

gene therapies is increasing, and it's going to continue to increase and it's going to increase rapidly. And their IT environment right now is fragmented, it's not current, it's not modernized. And while it can take advantage, and absolutely are and will be taking advantage of all of these FDA modernization, there are biologics specific things that must -- that lift needs to be there. There are biologic-specific things that must be taken into account.
The process, the trains need to keep running while this modernization takes place. And this commitment recognizes that and provides additional resources to support that data and technology modernization to lift it from -- give it the lift to get beyond the current stage of spending all of their time trying to maintain an old architecture to being able to use and…
It also references and recognizes that there is a need for resources to develop additional expertise and capacity for CBER and CDER and contracting resources to support and manage the increase in the volume and the diversity of bio informations data and computation biology information that is coming in, and regulatory submissions. This commitment acknowledges

Page 81

that and supports that so that FDA can continue to do and to improve on the -- and I see that I'm coming in a little choppy. I don't know if it's my voice or if it's -- again, I apologize for that. I'm not sure what to do about it.
MR. THOMPSON: You sound better now actually.
MS. SLACK: Oh, you're coming in choppy too. It's probably my audio, I apologize.
The benefits of all of this obviously are to enhance and improve our ability to operate for CBER, to enhance the support of complex biologics for FDA writ large and for the PDUFA program, its improved knowledge management, harmonizing with existing activities, improved data access and management and analytics. And I'll just stop right there and hand it back to Graham and Lucy and Cartier.
MR. THOMPSON: Thank you so much. Lucy and Cartier, you're on.
MS. ESHAM: So, thank you Mary Ann. And again -- oh, sorry I believe you're going first, Lucy. My bad. Go ahead, Lucy.
MS. VERESHCHAGINA: No, that's fine. So as Mary Ann said, the technology and data modernization effort has been a priority for FDA over the past few years, and industry strongly supports these efforts.

Page 82

And specifically Digital Health Technologies and its increased use in regulatory decision-making being a topic that generated a lot of attention and discussion over the past couple of years.

So, industry, we as industry, we're very excited about this efforts in PDUFA VII and about the opportunities for FDA to work with all the stakeholders on this issues, particularly on the public workshops, on the use of Digital Health Technologies for regulatory decision-making.

And I would like to stress that patient input will be critical here to make sure that we're able to successfully integrate the tools into drug development and regulatory review processes.

Second, I would like to stress the importance of regulatory consistency and coordination across FDA. And PDUFA VII includes some provisions to make sure that FDA is able to promote that consistency with regards to DHT-based policy procedures, and analytical tool development.

Also, I think that's another example where industry and FDA will be able to leverage some of the emerging COVID-19 lessons learned where appropriate, and we'll see multiple examples, how Digital Health Technology has been used during the pandemic by

Page 83

necessity, right, specifically for remote data collections, increased use of wearable technologies. And we as industry think that these tools have a lot of potential to build leverage beyond COVID, including, as Mary Ann mentioned, for decentralized clinical trials. I think those trials have a lot of potentials, including for increasing diversity in patient populations, participating in clinical trials.

And we believe that the digital health technology tools have the potential to enhance participation from communities that historically were not able to benefit from clinical trials. Of course FDA and industry needs to analyze those lessons we learned and then translate this information on DHTs used during pandemic into more durable learnings when appropriate beyond the pandemic. I'll stop here, Cartier.

MS. ESHAM: Thank you, Lucy. And again, thank you, Mary Ann for a great presentation. And just to underscore, there was a significant amount of work that went into coming up with the sections of the commitment letter, and they are extraordinarily important as we think about how to best ensure the FDA has the capacity and resources it needs to meet the growing demands of regulatory review of complex and very large data sets.

Page 84

And so, the data and technology, I'm just going to underscore a few things, the data and technology monetization strategy commitments that are in the letter were done in a very thoughtful manner. And that is to best ensure that the significant resources that are required are able to be used in the most effective way possible.

So as part of the commitments to achieve and that go along with this publication, and implementation of this modernization strategy, there are a number of engagement and assessment processes that will ensure that there's sort of an iterative approach as these capacities continue to get built and implemented.

It includes some very specific commitments such as completing transition of the ESG to the cloud. It also allows for assessment of challenges to the adoption of cloud-based technologies, but looking for and identifying solutions to those challenges by demonstration projects.

So again, I think when you read this in detail, I hope that it is clearly reflected that this was done in a very thoughtful manner. I'll also underscore the import and agreement that that resources were required to ensure that CBER had the data and IT capacity that it needed. So again, the data and

Page 85

technology modernization strategy, we are viewing that as an enterprise-wide a CDER, CBER wide activity. But CBER did require and needed some specific resources to ensure that they are best able to meet the demands of the data and IT needs to review biologics.

And lastly, we also provided some resources to ensure -- to build, to create stronger capacity for bioinformatics and computational biology needs. And so, this will help support reviews and submissions containing a variety of biologic data such as next-generation sequencing. So again, we think this will ensure that both the industry and the regulator are aligned with the needs of modern drug development and review processes. With that, I'll turn it back to Graham. Thank you.

MR. THOMPSON: Okay. Thank you so much, everyone. All right. We're going to move into our last session before lunch, which is on finance. And our presenter for this topic will be Josh Barton, and you may start whenever you're ready.

Finance and Hiring Proposed Enhancements

MR. BARTON: All right. Graham, can you hear me?

Page 86

MR. THOMPSON: Yep, we can hear you loud and clear.

MR. BARTON: All right. Great. Thanks.

Hi, good morning, everybody. Thanks to all the attendees who were able to join us today. My name is Josh Barton. I'm the Director of the Resource Capacity Planning staff in CDER, and I led the Financial Group for FDA.

I'm going to speak first to the financial topics in the agreement and then I will also speak to the hiring topics. While the hiring topic was not primarily under the remit of the financial group in the PDUFA VII process, both areas are really foundational to ensuring the continued success of the PDUFA program and providing the resources and expertise needed to implement the new PDUFA VII enhancements described by my colleagues earlier today.

If we go on the next slide, in PDUFA VII the financial topics were focused on building the -- financial building on the financial enhancements that were implemented in PDUFA VI, to advance the sustainability of the PDUFA program resources and to enhance the operational agility of the PDUFA program. Topics included resource capacity planning, financial transparency, and some updating to the fee setting

Page 87

process.

So, first speaking to resource capacity planning. So resource capacity planning is a capability designed to use data and analysis to help inform resource needs for the PDUFA program. The concept for this capability really grew out of the PDUFA VI negotiations, which included commitment to establish the resource capacity planning capability, to modernize our time reporting approach and to establish a new methodology to address review workload needs, which is called the capacity planning adjustment.

In PDUFA VI, we implemented these commitments, including the time reporting about the foundational RCP, Resource Capacity Planning capability, and establish the new methodology for the capacity planning adjustment. The PDUFA VII commitments are largely focused on continuing to mature the Resource Capacity Planning capability.

As we collect more data on resource needs and refined methodologies for forecasting review workload, the resource capacity planning capability will continue to mature.

In addition, across PDUFA VII, we will also be working to further integrate resource capacity planning analytics and the agency's resource and operational

Page 88

decision-making processes. The specific commitments in this area for capacity planning include publishing an implementation plan in the first year of PDUFA VII, which will outline our approach to the continual improvement of the capacity planning adjustment, how it will continue to mature the overall capacity planning, resource capacity planning capability, and how it'll integrate the resource capacity planning analytics in the agency's resource and operational decision making processes.

This is similar to PDUFA VI commitments where we published a implementation plan in the first year of the PDUFA VI program. You can also find a lot of background information on the agency's website on this topic, including that original implementation plan.

In addition, we'll provide annual updates on progress to this implementation plan in years 2 through 5 of the agreement, and we'll also document how the capacity planning adjustment funds are being utilized in each year's annual financial report. There will also be an independent third-party evaluation of the resource capacity planning capability which will be commissioned and published to the FDA's website in 2025.

Next slide. The financial transparency

Page 89

enhancements, these are primarily continuing commitments that were established in PDUFA VI to provide more transparency around our financial status of the PDUFA program. So, this continues the publishing of a 5-year financial plan each year as well as a public meeting to discuss the plan and other financial topics each year.

There are some additional commitments to public -- to address certain topics within that 5-year financial plan. And these two here, they really speak to the strategic hiring and retention adjustment, which will actually address on the on the next slide. But in terms of reporting requirements in the 5-year plan, we'll report on personnel compensation and benefits costs that exceed the funds provided by the PC&B, Personnel Costs and Benefits, portion of the inflation-adjustment.

As noted, this is related to the strategic hiring retention adjustment. And we'll also speak to the agency's plan for managing costs related to personnel beyond PDUFA VII. Next slide, please.

So, in terms of updates to the fee setting process, the annual fee setting process which is described in the Federal Register notice published at the beginning of August each fiscal year. There are a

Page 90

couple of -- a couple of updates or modifications to the process. The -- in terms of the capacity planning adjustment, which is that mechanism establishing PDUFA VI to account for changes in review workload needs.

There are some modifications to clarify the scope of the inputs used in the methodology. There's also the establishment of a new strategic hiring and retention adjustment to provide funding to cover costs for retaining and hiring highly qualified scientific and technical staff for the PDUFA program. And there are also some updates to the operating reserve adjustment process so that to help manage financial risks of the program, by establishing a minimum, a minimum amount of available operating reserves to be maintained each year.

So, this minimum amount would start at an amount equivalent to 8 weeks of operation in the first year of the program in FY '23. And that would step up to 10 weeks of operations by fiscal year 2025. Next slide, please.

So those are the highlights of the financial topics. And as mentioned, I'll also address the hiring. Hiring is an area that is, you know, critical to the continued success of the PDUFA program and the ability to implement the enhancements discussed earlier

Page 91

today, as hiring is really critical to ensuring we have the ability to hire and retain the necessary scientific and technical expertise to deliver on the program. So next slide.

In recognition of the criticality of the hiring and retention, under PDUFA VII, FDA will continue to report on hiring goals on the FDA website. And there'll also be a targeted third-party assessment of hiring and retention capabilities. This will be conducted by an independent contractor with expertise in HR operations and will be overseen by the directors of CDER and CBER.

This assessment will build on findings of previous evaluations conducted under PDUFA VI and will focus on improvements and remaining challenges. The assessment will be published in 2025. And will be followed by a public meeting to discuss its findings and the agency's plan to address any recommendations coming out of that report.

So that's the finance and the hiring. And with that, I can turn this back to Graham.

MR. THOMPSON: All right. Thank you so much, Josh. Cartier and Lucy, you're up.

MS. VERESHCHAGINA: Thank you, Josh. I can start. So in the standard update had whereabouts (ph)

Page 92

discussions of hiring and financials, just like in previous cycles, because we really want to make sure that all the great PDUFA VII initiatives that we include in the goals, whether it's actually implementable, and that FDA has supportive resources and technical expertise in place to work on all these provisions.

We also wanted to make sure that there is great public transparency and accountability around hiring and financials. And we want to make sure that all the PDUFA VI financial reforms that were put in place, continue to mature throughout PDUFA VII.

One of the examples that I would like to highlight is enhanced reporting. Specifically, issuance of the 5-year financial plan, and annual updates that as Josh mentioned will be posted. And the related annual public meeting.

Again, the opportunity for all stakeholders to review the report and provide the input and feedback to the agency and ensures there is transparency in place on programmatic financial measures. And again, allows for that public discussion of maturation of FDAs resource planning capabilities. So, I'll stop here and pass it to Cartier.

MS. ESHAM: Thanks, Lucy. Thanks, Josh.

Page 93

Again, you know, this is really the core of the entire PDUFA commitment mission, right. And if we're not able to provide the FDA with the resources it needs, and if the FDA is not able to onboard the resources it needs, then we're really not doing our jobs. And so these provisions are of critical importance both in ensuring that capability and ensuring that there is transparency, about how they're able to meet, how they're able to meet these commitments.

So, the one thing I'll underscore as an example of that is, one thing that was provided in the commitment is the ability for the FDA to utilize an independent contractor to do -- that has specific expertise in assessing human resource operations so that they can conduct a targeted assessment of the hiring and retention of staff.

It is the hope that these kinds of assessments provide important insights so that the agency is able to continue to learn and potentially improve upon the ability to recruit and retain the world class expert personnel that it has today and what we need to -- what we want to ensure that it has tomorrow. There will be a public meeting so that those insights will be available to the public. And we'll be able to hear about what the FDA is doing to address any

Page 94

recommendations that are part of that assessment.
So again, that's just an example of ensuring that there is transparency, the ability to assess and continue to learn, and hopefully continue to improve the FDA's ability to again onboard world class personnel that is of vital importance to ensuring they're able to meet their critical mission of protecting and promoting public health. So, with that, I will turn back to Graham and thank you very much.
MR. THOMPSON: Okay. Thank you so much, everyone. Our plan right now is to enter into lunch. We are well ahead of schedule. I don't think we need an hour and 15 minutes for lunch, but how about 15 minutes longer. So, we'll say a 45-minute break right now for lunch, returning here at 12:15 p.m. And we could send out a notification in the chat too, just to let people know. And maybe we can even take the slides down and edit that during this break, yeah. But 12:15 p.m. we'll see everybody back here. And thank you so much.
(Recess)
MR. THOMPSON: And we'll be beginning in just a minute.
MR. ABRAHAMS: Please, can someone confirm my audio is okay?

Page 95

MR. THOMPSON: I can hear you.
MR. ABRAHAMS: Thanks. Yes, I can. My video as well?
MR. THOMPSON: And for those who aren't speaking yet, if you don't mind being on mute. Thank you. I think we can go ahead and get started. Welcome back. Everyone have a nice lunch. We are going to move into our afternoon. And as we do so, I'd like to remind folks that if you missed the other part, the purpose of the meeting here is to gather input from the public on the proposed recommendations for the authorization of the Prescription Drug User Fee Act or PDUFA program.
If you'd like to contribute further input on this process, we've opened a public docket for those who wish to submit written comments. And for those who missed part of the early meeting, we will post the slides, a recording of the meeting and the transcript to our meeting website in the near future after the meeting.
Okay. So, we're going to move into our next session, which is to hear some perspectives from some public stakeholders. So we invited public stakeholders who are consistently active and engaged throughout our public stakeholder engagement process. And these four

Page 96

agreed to participate.
Our four speakers today will be Michael Abrahams, Cynthia Bens, Annie Kennedy and Ed Neilan. So, I'm going to give a little extra time. I'll say everyone has 10 minutes. And Michael, you are on deck first, if we could advance and load his slides. So Michael Abrahams is from Public Citizens Health Research Group, and you may begin whenever you're ready.

Public Stakeholder Perspectives

MR. ABRAHAMS: Good afternoon. I'm Michael Abrahams, senior health researcher at Public Citizen and I have no financial conflicts.
Next slide, please. We have many suggestions to improve the draft PDUFA commitment letter. Beginning with performance measures used to set goals for that program. The currently proposed measures we believe our simplistic timeline code is focused on pleasing the regulated industries desire for reviews. For example, at the top of the slide, I give one of those types of measures.
It is the percentage of new applications that are acted upon within a certain amount of time, in this

Page 97

case, 10 months. Instead of those sorts of measures, or in addition to those sorts of measures for performance, we think the FDA should develop and proffer in this commitment letter short and long term public health impact goals and measures. Things that give us information about how the FDA's decisions impact, you know, human health. And I offer on this slide at the bottom of the slide five examples of such of these measures. Let me just briefly highlight the first three.
We'd like to see these measures say something each year about how many applications are rejected in a way that allows the Agency to demonstrate to Congress and the public how good they did at playing defense for the American public for bad prescription drugs, and biologics. The second item on this slide at the bottom, we think that there should be tallies regarding warnings and withdrawals that result from approvals. That gives us a sense of where the FDA may have made some mistakes or missteps, when they approved medications.
And then finally the third item on this slide, a suggestion that the FDA regular report how often it uses gold standard evidence, randomized control trials, well-designed phase III trials as opposed to less

Page 98

robust types of evidence which have become all too common in the regulatory process.

Next slide, please. Related to FDA reviewer and advisory committee activities, we recommend that the Agency develop performance measures based on surveys of FDA reviewers and advisory committee members, and I've made this suggestion before. And these would be looking at the experience that these reviewers have reviewing NDA/BLA applications. Past surveys have been too infrequent and have had concerning results.

Just one example, in 2003 an HHS Office of Inspector General report found that among surveyed CDER reviewers, only 64 percent were confident in FDA decisions regarding the safety of a drug. Now, we think and feel strongly that candid FDA staff and advisory committee member perspectives on the adequacy of the Agency's review and decision-making processes are certainly germane to the performance of the program. And that should be measured and presented to the public and to Congress on a regular basis.

The kinds of measures that we're suggesting are at the bottom of this slide, and I'm just going to highlight the second one. It would be useful for the public to see the percent of reviewers at the end of

Page 99

the year who felt they were free from direct or indirect pressures from the regulated industry when they were reviewing applications.

Next slide, please. More generally, commitment letter language should be recast, revised, right, to emphasize the FDA's regulatory role, and responsibilities -- its regulatory role and responsibility. Presently, for example, it has prominent language in the commitment letter like this, and I'm quoting from the middle of this slide. And this is a quote from the commitment letter. "The goal of the program is to promote the efficiency and effectiveness of first cycle review process and minimize the number of review cycles necessary for approval, et cetera."

And we believe such language should be modified by adding that a primary program goal in addition to what's been stated, a primary program goal is to protect public health by minimizing the probability that unsafe or ineffective drugs or biologics into the market. It should be stated more over, the commitment letter should state that although the Agency offers technical assistance to sponsors in the preparation of their applications, important function that it serves, ensuring the quality of the

Page 100

application, and the data in it is ultimately the responsibility of the sponsor, not the FDA. The FDA is a watchdog for the American people.

Next slide, please. There are several places in the commitment letter were, "expediting drug development," is the clear goal, including under Section K of the letter, and I'm reading a quote from that section, it's on the slide here. "Enhancing -- ensuring the sustained success of the breakthrough therapy program is one of the goals. Use of new surrogate endpoints as a primary basis for product approval, and exploring real-world evidence for decision-making."

Okay. Such goals, we believe should be revised by adding statements, such as the fine. There should be limits to surrogate endpoint use to those that have been scientifically validated and deemed by the majority of the medical community to be predictive of clinically meaningful outcomes. It should be explicitly stated. It should further -- that is the letter should further caution that things like real-world evidence and other shortcuts to approval must not supplant well-designed randomized trials.

The need for these cautions and standards is supported by research which shows that as of 2018, 81

Page 101

percent of NDA approvals, evolved, accelerated fast track priority review pathways, not traditional pathways. And the faster approvals under PDUFA, other research has shown have correlated -- these faster approvals have correlated with the marketing of products that were less safe than those marketed before PDUFA was instituted.

Next slide, please. The draft commitment letter states the following. This is a quote right at the top of the slide, "FDA's philosophy is that timely interactive communication with sponsors during drug development is a core Agency activity to help achieve the Agency's mission, et cetera."

Okay. The FDA's review and approval of the BLA for Aducanumab for the treatment of Alzheimer's disease revealed, and we think it's the tip of the iceberg, that such interactive communications established under PDUFA have resulted in inappropriately close collaborations between Agency and sponsors that have compromised the integrity of NDA/BLA reviews.

To address this problem, the commitment letter should be modified to include provisions that do the following listed at the bottom of the slides, very specific recommendations. Characterize the FDA's

Page 102

primary role as being the gatekeeper, the watchdog and the judge of industry products. Not a partner, certainly not a financial partner.

This is to -- for the industry is an opportunity for FDA to reassert and to codify its objectivity and independence, so important we believe to the regulatory process. This letter should also establish procedures that separates staff involved in the pre-application submission interactions with sponsors from the staff that formally reviews and scores it.

And finally, the letter should require the FDA to establish staff training on how to minimize the risks of regulatory capture of agency sponsors.

And my last slide, please, slide number 7. Finally, here are several more actions the Agency should pursue as part of the PDUFA reauthorization process. I don't have time to go through all of them. I've gone through several of them in our stakeholder discussion meeting. I asked that staff take a careful look at them once again, but let me just highlight two for this audience currently, the second point on this slide.

The PDUFA reauthorization process should be used to -- or the commitment letter should be used to

Page 103

revise the reauthorization negotiation process to make the meetings between industry and the FDA fully open to the public. There seems to me and to many of us who have been at the table on the stakeholder side, there's no need for secret meetings separately between industry and the FDA to hash out this letter.

And skipping down into item number 5 on this slide, we think the commitment letter should create opportunities for the FDA to commission third-party objective studies that quantify the avoided or realized harm resulting from NDA/BLA approval decisions. This seems to us to be a critical public health reporting responsibility of the FDA. And it takes us full circle back to the beginning of my presentation where I've recommended some additional performance measures in that regard.

We encourage the FDA to use this presentation to substantially revise their commitment letter. My last slide has my contact information to facilitate that. Thank you very much.

MR. THOMPSON: Okay. Thank you very much, Michael. Next up, we have Cynthia Bens from the Personalized Medicine Coalition. If we can advance the slide. Cynthia, you're all set and if you're ready.

MS. BENS: Great. Good afternoon. Thanks to

Page 104

the FDA for the opportunity to share some insights on the importance of the Prescription Drug User Fee program, and also to reflect on the PDUFA VII goals letter. As Graham mentioned, I'm Cynthia Bens, and I serve as senior vice president of public policy at the Personalized Medicine Coalition or PMC.

For those who aren't familiar with this, PMC is a nonprofit education and advocacy organization that has more than 220 members from top sectors of health care, who are working together to advance personalized medicine in ways that benefit patients with cancer or diseases, some common chronic diseases and infectious diseases.

As you heard throughout the morning, the PDUFA program is really critical. And it's a source of funding that provides to ensure the timeliness of drug reviews, also to encourage innovation and drug development and promote initiatives at the FDA that leverages the best science. We believe that having a well-resourced, focused and flexible FDA is essential to achieving our mission at our organization of bringing forward the best treatments for each patient, and ensuring they're delivered based on a person's biology, medical history, circumstances and values.

PMC's analyses have shown that personalized

Page 105

medicines account for more than 20 percent of FDA's new drug approvals each year. That number steadily increased from 5 percent when we started looking at approval trends 16 years ago. Initiatives advanced by the FDA in recent years have fostered many notable regulatory firsts, including the approval of the first cell and gene therapies and a one therapies and tissue agnostic therapies.

We believe that enhancements included in the PDUFA VII goals letter will advance the future of personalized medicine, and will continue to yield benefits for a wide range of patients, including those with unmet medical needs. It's really difficult to summarize all the ways why PDUFA VII is going to make a meaningful change for the field of personalized medicine in less than 10 minutes. So, I'm going to focus on three main areas that we're pleased to see in the PDUFA VII goals letter.

These include staffing to support cell and gene therapy review, additional considerations for advancing the regulatory use of real-world evidence and real world data, and the use of digital health tools for regulatory decision-making and support of personalized medicine.

In comments provided at the beginning of the

Page 106

PDUFA VII process, we highlighted that FDA needed additional resources to fulfill the Agency's mission to protect and promote public health, while meeting the challenges posed by the increasingly complex regulatory landscape. This need is particularly pronounced in the area of cell and gene-based therapy review. Cell and gene therapies have the potential to yield unprecedented improvements in clinical outcomes for some disease areas. And they continue to be an important area for personalized medicine.

Just up until this point, 22 cell and gene therapies have already been approved by the FDA. And FDA anticipates that by 2025 it will be reviewing between 10 and 20 cell and gene therapies applications each year. We've been particularly concerned with the size of the workload facing FDA as a result of the need to evaluate the increasing number of new cell and gene therapy products.

PDUFA VII will allow the addition of significant numbers of FTEs across the FDA divisions by 2027. And it's reassuring to us that PDUFA VII resources will be devoted to addressing staffing gaps and building capabilities necessary to support the clinical assessment and evaluation of manufacturing processes for cell and gene therapies.

Page 107

PMC appreciates that in addition to expanding FDA's workforce that attention has been paid in PDUFA VII to furthering the development of appropriate regulatory frameworks for assessing the safety and effectiveness of these life-changing therapies. We at PMC also believe that data collected about an individual's lifestyle, their biology and treatment outcomes can be harnessed to complement traditional clinical trials and can help transform the future of personalized medicine.

In prior comments, PMC supported additional staffing, resources and guidance development under PDUFA VII to allow the Agency to make further transformations and we use an acceptance of RWEE beyond early phase trials and for purposes beyond demonstrating product safety. We are encouraged that PDUFA VII includes several RWE commitments, such as the proposed pilot program facilitating earlier advice on the quality and acceptability of RWE and supportive new labeling claims, a public workshop on RWE and updates to RWE guidance.

We want the Agency to move forward in a science-focused manner. But we also recognize that FDA is thinking on the use of RWE and RWD has been evolving for some time. RWE and RWD can make significant

Page 108

contributions in advancing all of our understanding of which patients will benefit the most from treatments. And this trend wasn't slowed down by the COVID-19 pandemic.

Out of necessity, nontraditional approaches to data-gathering and clinical studies were required to facilitate patient participation. Analysis also needed to be conducted on real-world data sources to more quickly understand treatment patterns for hospitalized COVID patients.

With the exception of the pilot, which begins early in the PDUFA VII cycle, the remaining commitments fall near the end, and we'd encourage FDA to accelerate their timeline for RWE and RWD commitments as it's feasible. It's promising that participation in the pilots contingent upon a willingness to publicly disclose elements of an RWE pilot submission. Depending on the level of disclosure, this type of transparency will allow stakeholders to more efficiently leverage real-world datasets.

But just given the limitations on the size of the pilot, and uncertainty about how much information ultimately will be disclosed, we'd also encourage FDA to provide additional venues for researchers, health data organizations, and other non-industry stakeholders

Page 109

to interact with the Agency on RWE and RWD issues.

Finally, PMC called on the FDA at the start of PDUFA VII to take steps that would accelerate the acceptance of digital health technologies and protocols for decentralized trials. Advances in sensing technologies and self-management platforms have become important tools for personalized medicine.

And in fact, a growing number of ongoing clinical trials feature the use of wearables environmental sensors to include more diverse populations, patients in difficult geographic regions and patients who cannot travel due to the ongoing pandemic.

We applaud the inclusion of several PDUFA VII commitments in establishing a framework for promoting regulatory consistency across the FDA on DHTs, increasing FDA's capacity in this area, and for hosting a workshop on the use of DHTs for regulatory decision-making leaving to DHT guidances. We believe that DHTs can enhance trial efficiency, parallel to the delivery of real-world care, and may even provide personalized insights at the point of care.

I'll close by saying that we know that much of what we highlight is potential areas for improvements at FDA with respect to RWE, RWD and DHTs won't be

Page 110

possible without continued modernization of FDA's IT infrastructure.

So, PMC supports the inclusion of PDUFA VII resources to increase the Agency's capacity to accept and review large datasets as existing needs dictate and also as new opportunities emerge.

So, thanks again to all of you for your time and for FDA for letting me participate. My PMC colleagues and I look forward to working with Congress as the PDUFA reauthorization process moves to the legislative phase. Thank you.

MR. THOMPSON: Thank you so much, Cynthia. Next up, we have Annie Kennedy, and, you know, your slides are loaded. All right. You can start whenever you're ready.

MS. KENNEDY: Super, thank you. Thank you for inviting me to present today on behalf of the EveryLife Foundation for Rare Diseases and our broader rare disease community. I'm Annie Kennedy and I serve as the chief of policy and advocacy for the EveryLife Foundation for Rare Diseases.

We are a rare disease policy organization that believes that no disease is too rare to deserve a treatment and rare disease therapies should be safe and effective. To that end, we convene a robust coalition

Page 111

comprised of patient advocacy organizations, biopharmaceutical partners, coalition groups and other relevant stakeholders with shared interests in policy focused on rare therapy development and regulatory infrastructure. These remarks are a reflection of the engagements of this coalition over the past few years.

I'd like to start today with a tremendous thank you. Thank you to the leadership and the personnel here at the FDA and those within our therapeutic development ecosystem. I think while the term unprecedented has probably been overused over the last 18 months, I'm not sure what other term we could use that would be appropriate for this forum here today to capture the climate of the forced evolution in which we've all worked and lived.

And we'd be remiss to not acknowledge the leadership and tireless work conducted by this Agency to protect our nation and our loved ones throughout the many phases of the pandemic. We are also grateful that while your capacity has been stretched to attend to the global pandemic, you also understood that the urgency of rare disease was not waning, but wasn't in fact, instead further exacerbated by the pandemic, and urgency that's being felt by the more than 30 million Americans living with rare diseases, a disproportionate

Page 112

percentage of whom estimated to be more than 50 percent of whom are children.

And as most here are well aware 95 percent of more than 7,000 rare diseases have no FDA-approved therapy. Yet the technologies and methodologies deployed during the pandemic by stakeholders here today that resulted from COVID-19 underscore the opportunities for innovations that have been long championed by our rare disease community stakeholders, and further reflected the core themes within the PDUFA agreements of scientific rigor, transparency, and stakeholder engagement.

So, from pivoting and deploying new innovations to protect our public's health throughout our COVID-19 pandemic, we thank you. But we also thank you for not taking our foot off the accelerator. Thank you for understanding that rare disease is also a public health crisis deserving of continued urgent attention. And that continued commitment to understanding is clearly evident in the PDUFA VII enhancements we're discussing here today.

So, I'd like to start with a bit of a broader focus and take a moment to reflect on the last 10 years. We as communities and collaborative stakeholders have experienced a tremendous evolution of

Page 113

patient engagement and related areas since their infancy in PDUFA V to their continued development via 21st Century Cures and PDUFA VI and now their continued maturation today.

And this time, the landscape has shifted for our rare disease community. We've seen a deepened engagement and understanding of the patient perspective via numerous approaches such as the patient-focused drug development meetings, both FDA-led and externally led, of the more than 70 PFDD meetings convened to date, at least half have focused on rare diseases.

We've had opportunities for meaningful participation in formal service on advisory committees, the formation and patient engagement advisory committee at CDRH reporting on the use of patient engagement information and reviews of approved products. We've benefited from the implementation of the patient experience data table in November of 2017 and further expanded in 2019, which enabled a new level of transparency and engagement between review division and relevant stakeholders around the integration of patient experience data within regulatory review.

And CDER issued -- the CDER issued a series of guidance documents for conducting patient-focused drug development have been critical tools in providing

Page 114

stakeholders with practices for collecting comprehensive representative input methods to identify what's important to patients, selecting developing and modifying fit for purpose clinical outcome assessment, and incorporating clinical outcome assessments into endpoints for regulatory decision-making.

And the numerous other guidances that are informing patient engagement and patient-focused drug development activities for drugs, cell and gene-based therapies, diagnostics and medical devices have been critical and have transformed our landscape. But most importantly are the lives changed and saved through products approved to treat rare conditions, especially those that have benefited from the inclusion of more robust patient insights and patient experience data is a part of the reviewing process.

And it's important to note that these approvals have not come because FDA has lower the evidentiary bar for rare disease products. Rather, they came because FDA and Congress have recognized the need for a nuanced approach to review of such products, given the unique nature of rare diseases, including patient populations, trial sizes and other critical data points and by instituting a structured approach to listen to the voice of the patient in a meaningful way.

Page 115

The FDA has demonstrated its commitment to science and to ensuring appropriate processes are in place to quantify the perspective of the patient and the caregiver.

The EveryLife Foundation is very pleased to see the FDA's commitment to advancing the field of patient engagement clearly evident in the PDUFA VII commitment letter released last month.

The rare disease endpoint advancement pilot, the STAR pilot, advancing patient-focused drug development within CBER and refining and advancing policies to support use of real-world evidence and innovative trial designs are all just examples of the commitments agreed to by FDA and industry that over the performance period will further support patient engagement in patients with rare conditions.

Given the promise and anticipation in innovative development and rare disease, we are particularly gratified to see the expanded emphasis on enhancing critical innovation areas through resources, public workshops, pilots and guidances to address emerging issues such as real-world evidence, Bayesian modeling and enhanced engagement formats such as the proposed proposals for Interact (ph), MIDD and the new type D meeting models.

Page 116

We are very pleased to see the priorities we've articulated throughout this process reflected in these commitments. We would also encourage that as we work towards further refinement of these commitments, we think about how we can incentivize and allow for collaboration between sponsors, the Agency and patient organizations on these critical concepts within the pre-competitive space, and not just when connected to a specific IND.

To a degree possible, we'd like to see FDA commit even more to advance rare disease policy, including by going above and beyond the commitments set in the letter, such as by exceeding stated deadlines. As an example, during PDUFA V, the FDA convened more PFDD meetings than what was put forward in the agreement, helping to significantly advance our field. The same type of commitment to do more is needed to today.

So, in conclusion, the EveryLife Foundation and our rare disease community are encouraged by the provisions within the PDUFA VII commitment letter. We are so grateful to all the community members who've worked so hard to ensure that the needs, priorities, opportunities and urgency of our community is so strongly reflected in these considerations.

Page 117

And our collective community organization partners are eager to continue to lean in and work with the agencies, sponsors, patient communities and Congress to ensure that communities' patient experience continues to inform considerations and decision-making all throughout the product development lifecycle.

Thank you for your tireless work on behalf of our rare disease community, and for your commitment to ensuring that the promise of today's pipelines will change the health outcomes for this generation of patients. Thank you.

MR. THOMPSON: Thank you very much, Annie. Finally, we have Ed Neilan from the National Organization for Rare Diseases (ph). If we can advance the slide. All right. Ed, if you're there ready, you can begin whenever you like.

MR. NEILAN: I was just trying to turn on the video. I don't know if you --

MR. THOMPSON: Well, we can hear you.

MR. NEILAN: -- (Cross talk).

MR. THOMPSON: We can hear you and you click the video button in the bottom left.

MR. NEILAN: I've clicked it a couple times. It says the host has stopped it. All right. Well, oh, there you go. There's a button for it. Thank you very

Page 118

much. Yeah, thanks.

Hello, I'm Dr. Edwin Neilan. I'm a pediatrician and a medical geneticist and the chief medical and scientific officer at NORD, the National Organization for Rare Disorders. Prior to joining NORD 4 months ago, I served on the faculties of Boston Children's Hospital and Harvard Medical School for 13 years and worked at Sanofi Genzyme for 4-1/2 years.

Collectively, I've worked on a dozen rare disease clinical trials which have led to six FDA new drug approvals. My professional focus is the care and treatment of patients with rare diseases. So, I'm delighted to represent NORD now, and to share here our views on proposed recommendations for PDUFA VII.

Next slide, please. Founded in 1983, NORD represents over 320 different rare disease patient organizations, and the over 30 million Americans who are struggling with rare diseases. We are committed to identifying, treating and curing rare diseases through programs of education, advocacy, research and patient services. This in support of and on behalf of our member organizations in the broader rare disease community that I speak to you today.

NORD was pleased to accept FDA's invitation to present at the prior July 23 meeting when Rachel Sher,

Page 119

NORD's vice president for policy, described our priorities for PDUFA VII. Since then NORD has participated in the stakeholder meetings and appreciates FDA's efforts to keep the stakeholder community apprised of the negotiations. I'm pleased to say that NORD's priorities are well reflected in the draft commitment letter. We are grateful to FDA and industry partners for your commitment to the needs of rare disease patients.

Let me describe a few of these priorities in more detail. Next slide, please. NORD was thrilled to see the inclusion of the proposed Rare Disease Endpoint Accelerator or RDEA Pilot Program in the goals letter. Establishing appropriate efficacy endpoints in rare diseases is often challenging because of a lack of regulatory precedent, small trial populations and limited understanding of disease natural history.

The RDEA pilot will provide sponsors with an invaluable opportunity to work closely with FDA at an early stage to overcome these challenges. Of note, the work that NORD has been doing as part of the ongoing Rare Disease Cures Accelerator, or RDCA, is in line with the goals of the pilot RDEA program and could help facilitate its ultimate success.

Led collaboratively by the Critical Path

Page 120

Institute and NORD, the RDCA data analytics platform or RDCA DAP is an FDA-funded project that will create a widely available data resource through which researchers, Android developers can access and analyze the identified patient level data on rare diseases and how they progress leading to new insights about those diseases.

Thus the work of the RDCA DAP can help foster the success of the PDUFA VII proposed RDEA pilot program by providing potential drug development sponsors even prior to the start of their own clinical studies with access to otherwise very hard to find patient level rare disease data, and associated statistical analysis tools that will allow sponsors to develop better proposals for the design and endpoints of their rare disease clinical trials for discussion with FDA during the pilot RDEA consultation process.

Next slide please. Another high priority in PDUFA VII is ensuring that CBER's results match the demands being placed on it. As we heard earlier cell and gene therapies hold great promise for the more than 7,000 rare genetic diseases. In recent years, there has been a dramatic increase in the number of gene therapy INDs.

Since 2018, CBER has been receiving more than

Page 121

200 INDs for cell and gene therapies each year. This is good news for rare disease patients. But to realize the promise of gene therapies, it is critical that FDA keeps up both in regulatory science and in its reviews of associated applications. On top of that marked increase in gene therapy INDs, CBER has now also experienced a massive further increase in INDs, many related to COVID-19.

At the end of 2019, CBER had over 900 active INDs. Then during 2020, CBER received 6,954 INDs. Under the proposed PDUFA VII agreement, CBER would receive 123 new FTEs. This further increase in staffing is essential. It will allow CBER to spend additional time on meetings with sponsors and on the review of submissions. But it will also permit FDA staff to engage in other equally important work like policy and guidance development.

In addition, as noted earlier, CBER's IT needs are also a concern. So NORD is encouraged that modernization of CBER's IT systems is also a goal in this PDUFA cycle.

Next slide, please. NORD is grateful to see that another one of our rare disease priorities is strongly reflected in the PDUFA VII goals letter that is better incorporating the patient voice into the drug

Page 122

development and regulatory review processes. NORD knows the value of FDA's patient engagement efforts having worked with FDA on multiple listening sessions and patient-focused drug development meetings.

Critical to the goals of patient-focused drug development is improving the availability of appropriate clinical outcome assessments or COAs. The goals letter describes FDA's continued commitment to developing a virtual catalogue of standard core sets of COAs, which NORD very much supports. This work is in line with both the project that NORD is engaged with, with C-Path to launch a broad new Rare Disease Clinical Outcomes Assessment Consortium, as well as other -- excuse me, as well as another FDA-funded project that NORD is engaged in with Northwestern University's clinical outcome assessment team or NUCOAT, which will develop and validate COAs with applicability across a range of both chronic and rare conditions by assessing physical function using both patient-reported and performance measurement outcomes.

Next slide, please. Finally, NORD also supports PDUFA VII's goal of ensuring that valuable drug development lessons and innovations learned during the COVID-19 pandemic are maintained. Given the scarcity of rare disease specialists, patients with

Page 123

rare diseases are often forced to take time off from work and to travel great distances to see their providers and participate in clinical trials.

During the COVID-19 pandemic, the use of remote monitoring digital health tools and other technologies that produce real-world data has enabled increased utilization of fully or partially decentralized clinical trials. These advances should become permanent fixtures in drug development, and NORD applauds FDA for taking steps to do just that. The commitments set forth in the goals letter around advancing RWE program and the digital health technology framework will be essential to achieving these goals.

Next slide, please. So thank you very much for this opportunity to share NORD's views on PDUFA VII proposals. NORD stands ready to continue our engagement on behalf of the rare disease community in the process of reauthorization as PDUFA VII moves to Congress. Thank you very much.

MR. THOMPSON: All right. Thank you very much, Ed. I believe that concludes the presentation portions of today's meeting. So, we're going to move into our final session, which is the open public comment. This is another important mechanism to engage public in the conversation.

Page 124

Keep in mind, we won't be responding live to comments, but they will be transcribed and be part of a public record, and a broken record on this. But please do submit any comments you have to the public docket, we do appreciate having them and -- yeah. So, to facilitate a transparent process, we do encourage speakers here to note any financial interests that you have that are related to your comment. If you do not have such interests, you may state that for a record. If you prefer not to provide this information, you can still provide your comments regardless.

So, we collected online requests for comment as part of the meeting registration process, and we have eight people signed up. Each speaker will have 5 minutes to speak. And as I stated previously, I'll verbally announce if there's -- if you're approaching your time, and then shortly again if you go over time.

So, the speakers -- if we can go to the next slide, the speakers will be in this order starting on the top left going down. So, we will begin with Robert Falb, if you are here.

Public Comments

MR. FALB: Hi, good afternoon. My name is

Page 125

Robert Falb, and I'm the director of U.S. policy and advocacy for the Alliance for Regenerative Medicine or ARM and I have no financial conflicts. We appreciate the opportunity to provide comments during this public meeting. By way of background, ARM is the leading international advocacy organization dedicated to realizing the promise of regenerative medicines and advanced therapies.

We are the voice of the sector representing more than 400 members worldwide. ARM appreciates the support that FDA has provided in advancing the development of cell and gene therapies and commends the Agency and the industry negotiators for their efforts that produced the PDUFA VII commitment letter. This is vitally important work and we know it is not easy.

It is a very exciting and critical time for the regenerative medicine sector. Scientific understanding of how to harness the potential of these therapies that are meant to cure some of our most devastating diseases continues to advance at a remarkable pace. With -- when PDUFA VI was reauthorized in 2017, ARM calculated that there were 580 advanced therapy developers conducting more than 480 clinical trials globally. Today ARM estimates that in the United States alone, there are over 1,100

Page 126

ongoing clinical trials. And globally there are additional 15,021 trials.

PDUFA VII recognizes the growth in this sector and takes many important steps to address the challenges that will confront the Agency in the coming years. It includes many different tools to share information and help improve communication between the Agency and sponsors. We are supportive of these initiatives as they are core to an efficient and effective regulatory review process.

However, a continuing concern to ARM and then when we -- and one that we have discussed previously with CBER is the increasing alliance on written responses to requests from cell and gene therapy developers to discuss important and oftentimes sensitive issues. Our member developers are utilizing cutting-edge methods and approaches that raise new complex community questions. We urge the Agency to grant more face-to-face or teleconference meeting requests, as they can actually be more efficient and informative for both the Agency and sponsor.

Timely and interactive CBER sponsor communications are vital if the full promise of these therapies is to be realized. A PDUFA VII top priority for ARM is to ensure that CBER has the resources to

Page 127

recruit, train and retain reviewers. We are very pleased with a commitment to substantially strengthen CBER staff capacity and capability. It is significant that of the 351 targeted hires for fiscal year 2023 through '27 for CBER and CDER, 228, or approximately 65 percent will be dedicated to CBER.

Another priority concern for ARM is the bottleneck caused by the CMC review of cell and gene therapy product applications, which the Agency has acknowledged accounts for approximately 80 percent of review resources. We are very pleased to say that the commitment letter includes several strategies to address this issue and are very supportive of the CMC development and readiness pilot program.

We urge CBER to move ahead expeditiously on all the CMC initiatives and implement the pilot as quickly as possible to help address the bottleneck. Furthermore, we encourage strong leadership and direction from CBER in establishing this pilot so that the unique challenges of CBER-regulated products are addressed.

We are also interested in the Real World Evidence pilot, Rare Disease Advancement Endpoint pilot and the STAR Pilot which all hold promise and could help in the advancement of drug development, especially

Page 128

those therapies targeting rare diseases. We encourage FDA to report out on the lessons learned from these pilots and what actions will be incorporated into regular practice and when.

ARM appreciates the Interact meeting formalization and the creation of the type D meeting, but stress that it is important how they are operationalized that will determine how valuable and effective they truly are. Regarding Interact, we would recommend that FDA track the number of requests made and how many are granted. We encourage CBER to actively engage in the Agency's implementation of these new meeting goals so that the benefits to advance therapy product developers are fully realized.

Patient engagement is an important aspect of ensuring that cell and gene therapies deliver on their promise. It is important to incorporate the patient voices, drug development and regulatory decision-making. PDUFA VII includes specific patient -- specific patient initiatives to ensure that this perspective is heard.

In conclusion, regenerative medicine sector is the next frontier in the fight against some of our most devastating diseases and disorders. These therapies have just begun to demonstrate their power to improve

Page 129

patient lives. And there's still much work to be done.

PDUFA VII will help to advance the field so these treatments can meet their potential and be more accessible to patients. Thank you.

MR. THOMPSON: Thank you very much, Robert. Next up, we have Brad Jordan. Are you here?

MR. JORDAN: I'm here.

MR. THOMPSON: All right. Floor is yours.

MR. JORDAN: Okay. Good afternoon. My name is Brad Jordan, and I'm the senior director of Regulatory Policy at Flatiron Health and independent affiliate of the Roche Group. I'm a Roche and a Amgen shareholder.

On behalf of Flatiron, I would like to thank you for the opportunity to comment today on the success of the PDUFA VII negotiations and to provide our recommendations for potential enhancements that will support the future use of real world data in the final agreement.

Flatiron Health is a health tech company dedicated to helping cancer centers thrive and deliver better care for patients today and tomorrow. We translate patient experiences into real world evidence to improve treatment, inform policy and advance research.

Page 130

Real world data and real world evidence can complement evidence from clinical trials to evaluate the safety and effectiveness of drugs and devices. It can help fill critical evidence gaps by capturing the experiences of patients who are not typically included in clinical trials, such as people with rare conditions or whose cancers possess rare genetic mutations.

There has been substantial growth in the use of RWE for regulatory purposes, and Flatiron has been proud to play a role in this growth and in pushing the frontiers of RWD sourcing, collection and analysis. We expect the use of RWE to continue to expand as new sources of data become available, and methods to collect, analyze and derive insights from these data continue to evolve.

As outlined in the PDUFA VII commitment letter, the advancing RWE program pilot for drug sponsors will establish programs that can improve the quality and acceptability of future RWE by sharing learnings from RWE submissions, and providing targeted regulatory guidance. Flatiron appreciates FDA efforts to advance the use of RWE, and we encourage the Agency to consider accelerating these efforts to establish these new programs.

In doing so, these programs can more rapidly

Page 131

lead to new understandings, new use cases for RWE, and more rapid incorporation of RWE into regulatory decisions. Additionally, we strongly support FDA's efforts to establish a digital health technology framework as now and in the future a variety of data sources and technology platforms may be combined to generate evidence to support drug approvals, endpoint development, and innovative trial designs.

A comprehensive approach to technology modernization is needed and should include input from stakeholders from across the health and technology sectors. As FDA considers public comments on PDUFA VII, Flatiron respectfully requests that the Agency establish a pathway to consult with data organizations, such as ours, who are generators of RWE to gain a greater understanding of methodological and technological considerations, as the role of RWE is further advanced for use in regulatory decision-making.

We welcome how the use of RWD is woven into many of the goals outlined in the FDA PDUFA VII commitment letter. In addition to the broader goal of advancing the use of RWE in regulatory decision-making through the pilot, FDA's goal to optimize the Sentinel Sentinel Initiative and develop the DHT framework will make use of RWD acquired through EHR systems or from

Page 132

other DHT-based measurements.

Also in the future, well-designed observational studies may be used to support post-approval requirements, for example, with drugs approved through the accelerated approval pathway. RWE organizations like Flatiron are crucial to advancing the use of RWD in ways that can contribute to the PDUFA VII goals and eventually realize the full potential of RWE as we play an active role in the collection and use of health care data.

Routine engagement with these organizations will enhance FDA's insights, submission, quality management and analysis in the near term, as well as help the Agency respond to changes in technology over time. Through broad stakeholder engagement and the Agency's transparency, organizations like Flatiron and sponsors that utilize RWD can better focus their development efforts to help ensure the success of FDA's modernization efforts and use of RWE to improve patient outcomes.

At Flatiron, we are constantly optimizing the collection, curation and use of RWE intended for regulatory decision-making. It is therefore extremely important to have a mechanism for data organizations like Flatiron to engage directly with FDA outside the

Page 133

scope of the drug sponsors development program.

In these cases, participation of a data provider in meetings with the Agency may be at the discretion of the drug sponsor. And therefore the ability to extract learnings and input from FDA on optimizing the use of RWD may progress at a slower pace. We therefore respectfully request that FDA consider a framework by which these direct engagements with data organizations can occur.

Thank you again for the opportunity to contribute our input and we look forward to additional opportunities for feedback in the PDUFA VII authorization process.

MR. THOMPSON: Thank you very much, Brad. Next up we have Paul Melmeyer. Are you here? Paul, are you -- if you can hear…

MR. MELMEYER: Yes, apologies. Can you hear me?

MR. THOMPSON: You're good. We hear you, all set.

MR. MELMEYER: Very good. Thank you very much. Good morning, and good afternoon, everyone. I am Paul Melmeyer with the Muscular Dystrophy Association and we serve the over 300,000 Americans with rare neuromuscular diseases, most of whom do not

Page 134

have an FDA-approved treatment indicated for their disease and even fewer of whom have a treatment that substantially alters the course of their disease. I have no disclosures.

We are here to offer a strong support for the PDUFA VII agreements and will support the enactment of the agreement in Congress next year and the implementation thereafter. There are several provisions included within the agreement that we believe will accelerate the development and approval of more and better therapies for the neuromuscular disease community. To start work today is meeting started. We are very pleased to see the influx of resources dedicated to CBER's gene and cell-based therapeutic reviews.

MDA's number one priority for this PDUFA cycle outlined in our August 2020 comments submitted to FDA and industry negotiators was a surge in resources for reviewing gene therapies. Our community knows the impact of these transformative therapies, the impact that these therapies can have as ZOLGENSMA, one of the very first gene therapies approved by FDA, has been substantially improving the lives of children with spinal muscular atrophy.

Furthermore, with gene therapies for Duchenne

Page 135

muscular dystrophy, Limb-girdle muscular dystrophy, Pompe disease, ALS and more in the pipeline, any unnecessary delay in developing, reviewing, and hopefully approving these therapies must be avoided. We hope these additional resources will accomplish this goal.

Second, we called for the consistent use of regulatory flexibility across the FDA when reviewing rare neuromuscular disease therapies. We called for the expansion of Oncology Center of Excellence programs to outside of oncology, including taking the O out of RTOR, and we're very pleased to see the proposed creation of the split real-time application review program.

And similarly, we see no reason why we couldn't similarly expand project facilitate outside of OCE as well. We hope further efforts to ensure consistent regulatory reviews across divisions are undertaken, either as part of this agreement by modernizing FDA's internal data systems or otherwise. As recent -- as a recent report highlighted, the varying approaches to assessing and determining substantial evidence of effectiveness used across the Agency.

Third, we called for further innovation on

Page 136

rare disease clinical trials. We called for further innovation on rare disease clinical trials. And we are very pleased to see the proposed creation of the rare disease endpoint advancement pilot program. Our community is no stranger to the use of antiquated endpoints with little connection to what is actually meaningful to the patient, as evidenced by the continued use of the six-minute walk test, the ALS, FRS, a handful of neuropathy scales, and more that are all rather outdated and do not reflect what patients actually view as meaningful.

We hope endpoints in neuromuscular disease trials will be included within this pilot. And we hope that the lessons from the pilot will not be limited to just a handful of development programs that are currently negotiated to be allowed under the pilot.

Fourth, with the advancements made in patient-focused drug development, over the previous two agreements, we called for taking these efforts one step further, by further facilitating the use of patient preference information and patient experience data and regulatory submissions. We're very pleased to see the inclusion of guidances and public meetings aimed at this very goal, as well as all the data collected in PFDD meetings and PFDD instructed studies, as with all

Page 137

the data collected in these studies. As such data can be most impactful when actually considered as part of a regulatory submission, perhaps even as confirmatory evidence.

Fifth and finally for today, we are very supportive of the innovations proposed for expedited review pathways, including the breakthrough therapy pathway and the accelerated approval pathway. We are pleased to contribute to a proposal put forward by Friends of Cancer Research and other colleagues that called for certain reforms in our expedited approval pathways, including moving beyond breakthrough and better integrating expedited development programs with the needs of CMC in innovative treatments. We're very pleased to see such considerations included in this agreement.

There's plenty more to say certainly, including on complex innovative trial designs, real-world evidence, decentralized clinical trials and more. But to stick to our time allotment, we'll include those thoughts in our written comments.

Thank you again for the time today.

MR. THOMPSON: Thank you very much, Paul. Next up, we have Jerry Roth. (Cross talk).

MR. ROTH: Hi.

Page 138

MR. THOMPSON: Hi. We can hear you.
MR. ROTH: All right. Let's see if we can get clicked in. Okay. Hi, I'm Jerry Roth. I'm representing Hill Dermaceuticals as one of the owners. We're a small manufacturing development company of topical products for adults and children. And I will be very brief.
I've been involved with the PDUFA fees, user fees since the inception in the early '90s. And there was -- this is one of the few -- I believe one of the few government programs that does not have any provisions of, you know, for small companies and I would like to say that not every company that develops is a multi-billion dollar company.
And I want to be very clear here. I'm not here -- I do believe the user fees, but I do believe the companies should not one-size-fits-all. And I also would like to be very clear that I believe the submission fee for NDA applications should -- I'm not talking of that and believe it should be any caps. I believe the Agency uses the same amount of resources to review one of our NDA applications as they do a big format application.
But what I like to refer to is the -- specifically is the facility fees and the product fees.

Page 139

At the present time, whether you have a -- if you're a $15 million company with a 20,000 square foot facility, you pay the same price, the fee to the Agency as, I won't mention any names, but big pharma company or multibillion-dollar company who may make 25 to 50 products.
And when I started here, I remember the first product fee was $5,000. The last time they separated these fees was well over 100 per product. And I would like for the Agency to consider and I'd like one point is they need to consider now or possibly slowing down the growth of the fees or the increase of the fees and have centralized this out for companies of different sizes.
I may -- I'm not the only one. I may be speaking for several companies, many companies don't speak up, but the percentage of fees regarding to the gross revenues is highly disproportional to the size of the company. And it's hard to, you know, to believe that the amount of resources on a smaller facility would be the same as on a multi-million -- multi-thousand square foot facility.
And lastly, that we'd like -- I believe this will be the first seed. I'm going to be here next year just to not complain, but to suggest that this -- that

Page 140

the Agency continue to consider this of possibly putting caps on small businesses for the amount of fees. And if when you compete internationally, it's very difficult to try to compete internationally and then pay the fees, you know, the continuing to rise in the United States or put on by the agency.
That being said, appreciate your time. Thank you and enjoy the meeting.
MR. THOMPSON: Thank you very much, Jerry. Next up we have Dru West. Are you here?
MS. WEST: Yes, I'm here. Turning to --
MR. THOMPSON: You may begin.
MS. WEST: I activated the video and the camera, I hope.
MR. THOMPSON: You -- yeah, we can see you and you sound fine.
MS. WEST: Okay, good. First of all, I want to thank you for the opportunity to speak today regarding the prescription drug user fees. My name is Dru West and I am the president of the USA Patient Network. We do not accept donations or support from any pharmaceutical or device manufacturers and we are completely independent patient voice.
As a nonprofit, we are composed of advocates who represent a multitude of other advocacy groups, who

Page 141

in turn represent thousands of patients, caregivers, and family members who have been helped and sometimes harmed by prescription medications and treatments.
Our members are patients and caregivers who are acutely aware of the urgency and need for effective and safe medications and treatments. The USA Patient Network values the important and challenging work that the FDA does to serve and protect our public health. And we are also grateful that there are individuals and companies in industry who want to develop drugs and biologics that will help people have healthier lives.
So, we deeply appreciate and understand that it takes both industry and the FDA to work together to bring safe and effective drugs to the public. Patients take medications because they're told that the medication or treatment offers hope, hope to cure or reduce the health impact of a medical condition.
That hope sits squarely in the face of patients and doctors and trust to the FDA to make sure that drugs are safe, effective and also hopefully affordable. The FDA is the guardian at the gate for safe and effective medicines and treatments.
Users fees have helped the FDA perform the goal of bringing medications and biologic treatments to the public in a timely manner. But paying a user fee

Page 142

should not entitle any applicant to a prolonged approval timeline or product on the market when a product no longer demonstrates clinical benefits.

We would like to see the FDA use its full authority as it continues to monitor and assess the safety and effectiveness of all products. In addition to industry asking FDA to complete timely reviews and approvals, we ask that the FDA set clear instructions and deadlines with industry for studies to be completed on a timely basis, and when necessary to remove medications that are not proven to be effective and safe.

We are encouraged the FDA wants to strengthen assessment of effectiveness and safety through as many meetings as possible and not just through MedWatch system or the Sentinel Initiative. We support ongoing consistent assessment of current safety monitoring tools for improvements. We ask that safety information be easy to access in understandable language be available to the public.

We are particularly concerned about the medications approved through accelerated approval pathway where a surrogate marker has been identified for approval of the drug. If the goal of accelerated approval is faster access to treatments that offer

Page 143

meaningful advantage to patients with serious conditions, then it is equally important that confirmatory trials be completed in a timely manner to confirm there actually is a meaningful advantage.

We ask that the FDA use the full power of its authority to insist that post-market commitments be completed in a timely manner, or to withdraw a drug from the market if a sponsor does not complete report confirmatory studies with due diligence, or if a study fails to confirm a drug's clinical benefit.

To maintain the trust and hope in the FDA, we ask in addition to -- in addition to performance scores based on speed of approval, that the FDA self-monitor and evaluate its own drug approval decisions and actions as to the real safety and efficacy, and to share this information with the public on a regular basis.

Not only does the FDA need to know how its decisions affect the public health, but the public needs to know that their faith and trust in the FDA is rightly earned. We are pleased to hear that the FDA's increased support for patient engagement in the PDUFA VII letter and we hope -- and we ask that consumer and public health advocates be allowed to attend or at least observe the FDA meetings with industry during

Page 144

reauthorization negotiations.

Because we believe that having firsthand knowledge is vital for safe production of drugs, we ask that in-person manufacturing facility inspections be the standard to monitor product manufacturing, and that they be resumed as soon as possible. We also ask the pre-market safety concerns be resolved before drug approval rather than relying on the use of volunteer REMS strategies afterwards.

Again, I want to thank you for the opportunity to share the USA Patient Network's concerns at this meeting. And I look forward to the process that continues. Thank you.

MR. THOMPSON: Thanks very much, Dru. Next up, we have Kim Witczak, if I'm pronouncing that correctly.

MS. WITCZAK: Yes, you did. Good afternoon. Can you see me and hear me?

MR. THOMPSON: Yeah, audio and video are both good.

MS. WITCZAK: Great. Good afternoon. My name is Kim Witczak, and I'm speaking on behalf of Woody Matters, a drug safety organization started in 2003 after the death of my husband due to an undisclosed side effect with antidepressants. Woody Matters

Page 145

represents the voice of thousands of families who live everyday with the consequences of the current drug safety system.

We make sure the real-world patient perspective is represented in health care conversations, such as the one we're having today. I am also on the board of directors for USA Patient Network, an independent patient voice advocating for safe, effective and accessible medical treatments. And I have no financial conflicts of interest.

Over the past year-and-a-half, the pandemic has highlighted the need for having a strong regulatory agency that can respond quickly. It has also shined a light on other things such as issues with conflicts of interest, political interference, and the importance of a strong safety mechanism when it comes to our medical products.

This is my third PDUFA authorization cycle that I've participated in. In reviewing the draft materials for today's meeting, I would like to make the following comments. The priority -- oops, sorry here. The priority once again seems to focus on expedited and speedy approvals. With the public being the ultimate end consumer of the FDA-approved products, performance goals should be based on safety and efficacy, not just

Page 146

speed. It shouldn't be an either/or proposition.
I get it, the industry expectation of FDA is to approve their products quickly so they can get on the market faster. But sometimes this is at the expense of safety. And obviously COVID has highlighted the pressure and public's desire for speed as well.
As a consumer representative on the FDA's Psychopharmacologic Drugs Advisory Committee, almost every drug that has come before our committee has had some sort of fast-tracking pathway like breakthrough therapy, accelerated approval, priority review for an unmet need, and have used the REMS program as a catch-all for safety.
In my opinion, we need to stop relying so much on the voluntary REMS strategy to flag safety issues instead of focusing on pre-market resolution of safety concerns. Everyone knows that the voluntary REMS are very rarely effective. We also need better, quicker response and communication of adverse events and harms.
I still support a previous idea of separating staff responsible for pre-market approval and from post-market safety. We need a proactive surveillance from a variety of sources unlike what we're witnessing, playing out in real time with the COVID vaccines. There needs to be an attitude of safety first, and a

Page 147

desire to actively investigate reports of harms versus quickly dismissing or disregarding them as not related to product.
We also -- number next, we need to leverage resources to fund outside non-conflicted experts, consultants and make investments in upgraded technology that is designed to detect -- to detect a big or detect and aid in proactive surveillance.
We need to redesign the FAERS MedWatch system. This is an important post-market safety tool with a big data solution that can be easily customized to capture many fields of information. It needs to allow someone to view and search all reports by a key word in the report, then an algorithm can be built that can connect a string of words together.
The other thing that's desperately needed in this system is a public facing as -- so that the data tools available to anyone, it needs to be intuitive and user-friendly. We need to be able to see who reported on the event. Was it patient-reported, physician, hospital, manufacturer-reported? It also should include the patient narratives in the reports.
Right now we're only able to see codes and not really the story of what happened. The technology and solutions are out there and it doesn't need to take 60

Page 148

million and years to build. It all comes down to motivation. And as I always say when it comes to safety, it's only as good as the motivation and intention behind it.
I strongly support the FDA staff and retention efforts because we need the FDA to do this important work. They need to have the space for free thinking and ability to debate over everchanging science. Unfortunately, right now with the vaccines, it has also seemed to become a political environment. Politics should not be driving these decisions.
Next, I would like to -- I also appreciate the FDA's ability to pivot during the pandemic. But now we need to get back to in-person inspections, as well as I would love to see Adcom meetings with remote options continuing.
And finally, there has to be a culture of openness and transparency within the FDA. There should be no closed-door meetings when it comes to PDUFA. The public should be included in these initial and negotiation meetings. I'd also like to see a concerted effort involved in getting different types of patient and consumer voices. It's important to get the real-world middle of America patient who has no agenda or financial interests. Their voices are often drowned

Page 149

out by patient and consumer groups supported by industry interests.
Lastly, we need annual performance reviews of FDA's ongoing work. Specifically, it'd be great to know the number, percentages of drugs approved that were subject after approval with warnings or withdrawals, or number of drugs that are using the gold standard of having at least two phase III placebo-controlled trials or an update on the drugs with REMS at the time of approval.
I know as a consumer rep, I would love to hear and learn more about the status of the drugs that we have previously approved on my committee. At the end of the day, we all need a strong FDA, one that is based in science and not politics, and ultimately sees the public as its customer and not just a partner servicing the industry. We need -- we all need a good watchdog.
So, I appreciate your time and being open-minded when considering my comments and others that you're going to be hearing during the process. Thank you.
MR. THOMPSON: Thank you very much, Kim. Next up, we have Diana Zuckerman. Diana, are you here?
MS. ZUCKERMAN: Can you hear?
MR. THOMPSON: Okay. We can hear you. You're

Page 150

all set.
MS. ZUCKERMAN: Okay. I'm trying to be visible as well. I'm not sure this is going to happen.
MR. THOMPSON: Oh, yeah, it looks like it's working. Oh, we just had you and then we lost you. There you go.
MS. ZUCKERMAN: Try and (inaudible). Okay? Can you see me?
MR. THOMPSON: Yeah.
MS. ZUCKERMAN: I can't see myself. I'm hoping it works.
MR. THOMPSON: We can see you. You're all good.
MS. ZUCKERMAN: Okay. Great. Hi, I'm Dr. Diana Zuckerman, president of the National Center for Health Research, which is a patient-centered public health think tank. I'm -- I appreciate the opportunity to speak today. And I'm going to focus on some of the same issues, but also some different issues that we've heard about.
In addition to speed, PDUFA performance measures need to evaluate whether patients are protected from ineffective or unsafe products being approved. As Commissioner Peggy Hamburg said, "Innovation needs to be in products for better, not

Page 151

just new." The performance goals have fallen short because the emphasis has been really only on speed and ease of approval, not on the quality of the outcome of FDA reviews, or of the products themselves.
PDUFA has resulted in more and faster approvals and it's been a great success in that way. But not all those approvals have helped patients, and some have seriously harmed them. Premarket performance should also include evaluations of the percentage of applications that were rejected or withdrawn because there was a lack of evidence proving safety or efficacy, and should also evaluate the specific reasons why.
It's that kind of transparency that will really help patients feel like they know what's going on at the Agency. When post-market surveillance works, it sometimes should result in FDA warnings, recalls or withdrawals and FDA should again provide the percentage. In this case, how many of these actions were taken for the 5 years after approval and the reasons for those actions. Again, that's the kind of performance that helps us understand how well things are working.
Performance should also include the percentage of products that are approved based on at least two

Page 152

well-designed studies. And in most cases, these are going to be phase III randomized controlled trials. As an epidemiologist, I love big data. But it's very hard to use big data for products that haven't been on the market yet. So, for that reason, randomized controlled clinical trials are still going to be really important in the pre-market space, as well as the post-market space.
The percentage of approved products that are subject to mandated post-marketing studies, and the percentage where those obligations were fulfilled is really important to know. We need to know were they started and ended on time, were they conducted as promised and as required, and did they or did they not confirm the safety and efficacy of those products.
And your -- FDA recently had a meeting on some cancer drugs that had indications that for several years have been known not to have been confirmed, and yet those indications stayed in place for several years. It's that kind of activity that user fees should be -- should help speed things up.
A newly published study indicates that too often a rejected application is subsequently resubmitted and approved when FDA ignores their own criticisms of the original application, even when those

Page 153

criticisms remain valid. The controversial approval of Aduhelm is just the most salient example of that.
And I would just like to say a few words about the commitment letter. The commitment letter changes policies and policies should be publicly debated by Congress and should include input from patients, consumer and public health advocates as part of any decision-making and any negotiations. Policies should not be negotiated behind closed doors at meetings that exclude these important perspectives.
And now I just have five specific suggestions. Patient preferences and involvement, and we were very happy to hear efforts underway to improve those. But they should always include harmed patients, not just patients who have been recruited by industry, and who very often are the patients who are really desperate for treatment. We all understand that desperation. But all patient perspectives are important, including patients who've been harmed.
Voluntary REMS strategies, as you know, are rarely proven to work. REMS needs a complete overhaul or REMS should be avoided. Instead, most safety concerns should be resolved before the products are approved. And just mention FDA's own analysis of opioid REMS has shown how ineffective that was, and

we've all paid the price for that as a country.

Number three, the commitment letter should implement the National Academies public health framework for regulatory oversight of opioids. Number four, in-person manufacturing inspections do remain the most effective way to determine problems. And for that reason, although remote inspections were absolutely needed during the pandemic, they should be the exception moving forward. They should not take over for those in-person inspections.

And number five, user fees should fund independent objective studies to assess and quantify the harms that resulted or were avoided due to the approval decisions that FDA made. I just want to add one more thing. I was very glad to hear today about trying to enhance the Sentinel project. I've been a strong supporter of those kinds of big data. But, so much money has been spent on them, so many years have gone by, and it's distressing to hear that there's still efforts underway trying to figure out how to get that -- those data sets to actually be objective, useful pieces of information.

And my last remark is just to say, again, I quote Peggy Hamburg that she saw the FDA as a public health agency, I think all of us who admire and respect

the FDA continue to see it as a public health agency. And we want to make sure that the user fees aren't interfering with that public health mission.

And unfortunately, when decisions are made behind closed doors, it's very hard to feel confident about the public health mission. Thanks very much.

MR. THOMPSON: Thanks very much, Diana. I'm definitely going to get this name poorly, but Nishan Yau (ph), are you here? Yeah, we hadn't had confirmation that they were going to be able to attend today, so. I think with that, we will move to the end of the public comment period, and move to the end of the overall meeting.

So, thank you to all the public commenters in both the last two sessions. This concludes our public meeting on the proposed PDUFA reauthorization. We very much value all the input that's been generated from today's discussion. We look forward to receiving further comments on the public docket.

Again, as a reminder, the recording for this meeting and the slides and a full transcript will be posted to the PDUFA VII webpage. And with that, thank you all very much for attending and have a great rest of the day.

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