SCIENCE BOARD TO THE

FOOD AND DRUG ADMINISTRATION

VIA WEBCAST

2:00 p.m.

Tuesday, May 9, 2017

FDA White Oak Campus

Building 31, The Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland

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P R O C E E D I N G S

[2:02 p.m.]

DR. McLELLAN: Good afternoon, everyone. I hope you are all enjoying a beautiful day. We are here up now in the mountains. So good afternoon.

Let me remind everyone that you have signed in now to the Science Board for FDA. This is our May 29th meeting. I would like to first give you some guidance here about silencing your cell phones, smart phones, and any other ringing devices that you can think of. We would appreciate that, if you would put those on silence.

As this meeting is being conducted by webcast, we would ask you to please speak clearly, slowly, and, of course, be sure to state your name before speaking so that the transcriber can capture the fact that it is you speaking and what your thoughts are.

My name is Mark McLellan. I am the chairperson of the Science Board for FDA. I will be chairing this meeting, and I will now be calling the Science Board meeting to order.

I will start by running down the roster of the Science Board members. If you are present online, please unmute your phone and say "present."

Cynthia Afshari?

DR. AFSHARI: Present.

DR. McLELLAN: Tony Bahinski?

DR. BAHINSKI: Present.

DR. McLELLAN: Lynn Goldman?

DR. GOLDMAN: Present.

DR. McLELLAN: Annalisa Jenkins?

DR. JENKINS: Present.

DR. McLELLAN: Barbara Kowalcyk?

DR. KOWALCYK: Present.

DR. McLELLAN: Lisa Nolan?

FEMALE SPEAKER: She will be here. I have her phone dialed up for her.

DR. McLELLAN: Great. Thank you.

Bruce Psaty? I am aware that Bruce is not able to make it today.

Ted Reiss?

DR. REISS: Present.

DR. McLELLAN: Minnie Sarwal?

DR. SARWAL: Present.

DR. McLELLAN: Thank you.

Scott Steele?

DR. STEELE: Present.

DR. McLELLAN: Laura Tosi?

MR. RAGHUWANSHI: She is on the line, Mark.

DR. McLELLAN: Okay.

Connie Weaver?

DR. WEAVER: Present.

DR. McLELLAN: Sean Xie?

DR. XIE: Present.

DR. McLELLAN: And Mike Yaszemski?

Sounds like we do not have Mike Yaszemski with us either.

Rakesh, I think you can establish the fact that we have a quorum? Can you confirm that?

MR. RAGHUWANSHI: Yes.

DR. McLELLAN: Very good.

DR. TOSI: I apologize. I am back.

DR. McLELLAN: Very good. Who was that again? I am sorry.

DR. TOSI: Laura Tosi. Sorry.

DR. McLELLAN: Laura. Very good.

As I mentioned in my guidance to you regarding today's meeting, we will follow pretty close to traditional Robert's Rules. We now have our meeting called. We do have a quorum.

We have an agenda in front of us. Each of you should have received that agenda. If there are any concerns on the agenda or changes to it, now would be the time to speak.

Hearing none, we will declare the agenda as set.

This meeting is always transcribed in full, and I would direct anyone considering or concerned about the prior meeting's minutes to take a look at the transcription that is posted online and any other summaries of the minutes. If there are any concerns about prior minutes, again, now would be the time to voice those concerns.

Hearing none, we will declare those minutes as having been established and proceed into our meeting today.

I guess I would like to clarify some of my earlier guidance regarding the agenda today. We will be looking at a review of the work plan. This is not a formal approval. We are asked specifically to provide guidance.

So the motion will eventually, after the FDA presentations, will be a motion to review. We will seek a second and move right through the process.

So with that, I will turn this over to Rakesh for his guidance to us regarding conflict of interest, and then we will move into the FDA presentations.

Rakesh?

MR. RAGHUWANSHI: Thank you, Mark. Thank you to all those who took the time to dial in.

Good afternoon to everyone. Welcome to the

members of the Science Board, the public, the FDA staff here in the room to today's Science Board meeting.

Today, the Science Board will review the FDA's Innovation Projects work plan ahead of the agency's submission of that work plan to Congress.

All members of this advisory committee are special government employees and are subject to Federal conflict of interest laws and regulations. The following information on the status of this committee's compliance with Federal ethics and conflict of interest laws covered by but not limited to those found at 18 U.S.C. 208 is being provided to participants in today's meeting and to the public.

FDA has determined that members of this committee are in compliance with Federal ethics and conflict of interest laws. Based on the agenda for today's meeting, no conflict of interest waivers have been issued in connection with this meeting.

We have one open public comment period scheduled for around 3:55 p.m., although that portion of the agenda may come slightly sooner, depending on our pace this afternoon. There has been one request to speak. Please remember to unmute your phone when speaking and state your name for the record so the transcriber can pick it up, and mute it when you are finished, to help

minimize background noise.

I will also echo Mark's comments at the beginning, to make sure your phones are off or on silent, so as to minimize disruptions.

Thank you very much.

Mark?

DR. McLELLAN: Very good.

So just a reminder of what we have ahead. It is to be a fair and open forum of discussion. As Rakesh said, we will have some public comment.

I would like to just I guess give you a general reminder that we want individuals to be able to speak into the record, but please be recognized by the chairperson, myself, and let's just try to work our way through this. I know it is a little bit difficult when you are remote and all we can do is have an oral connection here.

As we do go through the final evaluation looking for discussion, I will be using the role of the committee members and walk through that to make sure that I am hearing as much input as possible. If you do need time to craft your thoughts regarding any one section we are on, simply indicate, "Mark, can you come back to me?" and I will do that. And if I fail to do that, just send an oral kick to my shins, and I will be

sure to come back to you.

I remind you, in the spirit of the Federal Advisory Committee Act and our Sunshine Act, that we really want all of our discussion regarding our activities to take place inside our formal meeting. And so anything that might have been done prior, anything that might be afterward, these are secondary to what we are really asked to do, and that is to provide guidance right now.

So we have gone through the conflict of interest. Let's go ahead and start with our FDA presentations.

Let me invite Malcolm Bertoni to step up. Malcolm and I had a great conversation to set the stage for this. I really appreciate his understanding and awareness of the details around this. Malcolm is the associate commissioner for planning.

Malcolm, thanks for being here with us.

MR. BERTONI: Good afternoon. I want to reiterate FDA's thanks to all of you folks on the Science Board for supporting FDA in this effort. We greatly appreciate your help in conducting this review on a timeline that should allow us to submit the final report to Congress by the statutory deadline.

We are going to present an overview of the work plan today. I am going to start off with some general

remarks about the process that with maybe some review, but just to make sure that everything is clear to everyone listening and on the record. Then I am going to invite a few of my colleagues to talk a bit about some of the key provisions of the Cures Act that we are going to be implementing through the work plan and any subsequent funding that we may receive from it.

Just as a bit of background, we will be calling the 21st Century Cures Act the Cures Act or the act throughout today, so that is what we mean. This is an important new law that addresses a broad array of issues around health care, treatment, discovery, development, access, delivery, and resources. It runs over 300 pages. It was signed into law on December 13th, 2016.

FDA is a primary focus of Title III, Development, which includes important new authorities in the areas that are shown on this slide, such as patient-focused drug development; advancing new drug therapies; modern trial design and evidence development; patient access to therapies and information, including combination products; antimicrobial innovation and stewardship; medical device innovations; and improving scientific expertise and outreach at FDA.

Now Congress authorized $500 million to be

appropriated to FDA over 9 years to support the implementation of the law. We will talk a little bit more about the details of that in a moment. We thought it might be helpful to provide a picture of how the FDA provisions fit within the scope of the entire act and how the different funding streams work together to support this effort.

The Cures Act authorizes funds that are intended to support really a broad range of things, such as scientific innovation at NIH and State responses to the opioid abuse epidemic, among others. It does authorize this Innovation account that covers certain provisions in Title III.

Because the scope of the Cures Act extends and modernizes authorities that already fit within FDA's public health mission, there is some overlap between the activities that can be funded by the Innovation account and other funding sources that FDA uses to carry out our mission to oversee medical product development.

FDA is able to use its base budget authority funding to support Cures Act implementation. Also, Title III addresses areas of medical product development that fall within the statutory definition of review process activities that can be supported by

medical product user fees, so FDA can apply user fees to the implementation of many sections.

However, it is important to note that when Congress reauthorizes FDA's user fee programs, they are based on agreements negotiated with regulated industry about the performance commitments that FDA agrees to meet given the amount of user fees we are authorized to collect.

Consequently, dare I say every nickel of user fee money is planned out to support those performance commitments. So the overlap here is really only helpful to the extent that user fee negotiations anticipated the Cures Act requirements and incorporated them into their performance commitments. I just wanted to make it clear that even though there were some areas of overlap, that does not necessarily mean that there are additional funds to support these new responsibilities and authorities.

Now the actual requirement for developing this work plan that you are reviewing comes from Section 1002 of the act. We are required to develop a work plan that will cover how we would allocate the $500 million of Innovation Account funds over the 9 fiscal years covered by that fund. It does limit allocations to eligible activities authorized to be funded, which

is Title III, Subtitles A through F, and Section 3073.

As we are doing today, we are required to seek recommendations from the FDA Science Board on the work plan and the proposed allocation of funds. We will then consider the Science Board recommendations and submit the final work plan to Congress within 180 days of enactment. That is why we have been on this schedule to get this done as quickly as we could, and we are planning to submit this report in early June to Congress.

Looking at the evaluation of this, we wanted to share with you how FDA went about deciding how to allocate these funds. This was a challenging exercise for FDA for a variety of reasons.

I already mentioned the complexity introduced by the different funding sources. That complexity is compounded by the uncertainty introduced by the transition to a new administration and the uncertainty in how budget priorities are going to play out, as well as the uncertainty about the reauthorization of the user fee programs and whether the current draft legislation will pass as written.

Moreover, the Cures Act merely authorizes the Innovation Account funds. Those funds are subject to annual appropriations.

Given all these uncertainties, there is a wide range of possible scenarios regarding what levels of new funding actually may be available to FDA over the course of the 9 years contemplated by the work plan. To address these uncertainties, FDA considered the criteria on slide six as each program worked through its planning process and then came together as a group to finalize the allocations.

So you can see we looked at how the particular activity would present the greatest opportunity for FDA to foster innovation and integrate advances in biological sciences, engineering, information technology, and data science to most directly enhance the agency's product review tools and processes. We looked at how to address the greatest needs for scientific modernization. We looked at things that would have the most immediate impact on delivery of services to patients, the medical product industry, academia, and health professionals. And we looked at whether or not other funds might be available to support those activities.

So we now come to the charge to the Science Board, our request that you review the proposed work plan and provide recommendations for FDA's consideration. We have formulated that in two specific questions that

parallel the requirements in the act. The first question is, are the criteria used by FDA to prioritize the proposed allocation of funds appropriate? And the second is, are the proposed activities reasonably likely to contribute to successful achievement of the Cures Act requirements?

We thought that given all the uncertainties, and the need to revisit the -- on an annual basis as part of the appropriations process, that this would be an appropriate way to frame the question, to ask for your help in focusing on the criteria that we use in this repeated process, so that we can consider improvements and learn how to do better allocations over time.

Of course, we are also interested in your recommendations on the activities that we selected to fund. If you see relevant trends and developments emerging in your respective fields that may or may not be reflected in the allocations, we need to take those observations into consideration as we refine our plans going forward.

So in terms of our next steps after this meeting, we will consider your recommendations in finalizing the work plan. We will need to submit the final version through the Department of Health and Human Services and the Office of Management and Budget for final

clearance. After that, we will submit to Congress the final work plan along with your recommendations.

So that concludes my introductory remarks. I am going to invite my colleagues to come up and talk more about some specific areas of the act.

DR. McLELLAN: Thank you, Malcolm. That is great. It certainly showcases the overview.

As each of your speakers come forward, if they could introduce themselves and say a word about their specialty and background, we would appreciate that.

So I actually have listed here three presentations scheduled. I think we are going to be hearing from Doctors Mullin, Buckman-Garner, and Marks. Each of them focused on three major areas of the work plan.

Go right ahead.

DR. MULLIN: Thank you. This is Theresa Mullin. I am very happy to be here today to take a few minutes to talk to you about one of the provisions. As Malcolm said, the plan covers much more, but I am going to speak about one of the highlighted sections.

So I am the director of the Office of Strategic Programs in the FDA Center for Drug Evaluation and Research. I have been serving as the lead negotiator for the PDUFA reauthorization discussions for over a decade, I have to say, with mixed feelings. Also, I

have been the lead for CDER on the patient-focused drug development program, which you can see on the next slide, which I will advance to.

Just to give the board a little bit of background, FDA had initiated a patient-focused drug development effort under the PDUFA V, so the fifth reauthorization of the User Fee Act that covers the period of fiscal years 2013 to 2017, and calendar years 2012 to 2017. It began as part of that commitment, actually as part of our benefit-risk commitment there.

The work that we have done over the past several years I think has truly provided a foundation, and it actually provided a great deal of interest from our external stakeholders both in industry and in the research community, and very much in the patient community, about extending this work. So I think that the provisions that we see in the Cures Act are a reflection of this. We were very happy to see these provisions included.

So just to continue with the background, and starting with the negotiations of PDUFA V where we had patient stakeholders also talking to us throughout the negotiations in separate sessions about their concerns, we understood and recognized the need to develop a more systematic way of gathering patient perspectives on

their conditions, on the disease they are living with and also the available treatment options. And we needed a way to inform our benefit-risk assessment with this very critical clinical context.

So we committed to conduct at least 20 public meetings, each focused on a different disease area. What made these meetings rather unique is that only patients and their caregivers were speaking at these meetings. They were informing us about their perspective. Everyone else, including FDA and any drug sponsors and others who came, were in listening mode.

Each of these meetings produces a Voice of the Patient report that tries to truly capture the way patients are describing their experience with their disease and what it is like to use the treatments that they are taking for their disease.

So these meetings have been very powerful. We have gotten a lot of very good feedback about them. One of the questions that came up a lot is, what is next? What can we do beyond these meetings? How can FDA use this information? We realized that this was just a starting point to really make full use.

So we understood from this process that patients are experts in what it is like to live with their condition. And often, their chief complaints, as they

were telling us about these meetings, are not factored into drug development programs in a very formal way, such that the information that comes out of it can be used for regulatory decision-making.

So in that PDUFA VI negotiation, which we concluded last year, which we are closely watching the reauthorization discussions going on now in Congress, in this latest commitment that we hope will proceed soon with reauthorization, we have committed to developing a series of guidances that will help bridge from those initial meetings to a fit-for-purpose tool that can be used for collection of this kind of information during drug development and at other times, but will really serve to support regulatory decision-making.

So now you can see the nice overlap between that and the Cures Act Subtitle A of Title III. In the first section, they define what is patient-experience data. There you can see that it is really information that we need to make public about the patient's experience with their disease. The treatment burden and disease burden, and the benefits and risks are the terms that are used to describe the patient experience.

Starting this June, applications that come in and are submitted and later approved starting 180 days

after enactment, which would mean mid-June, we will begin to post a brief statement about the use of patient-experience data and related information with each approval decision, so that that will be clearer to the public about how that information is used.

And even more extensively and significantly, Section 3002 requires that guidance be developed addressing eight areas of interest. These are articulated in the statute.

The first is to address methodological approaches to be sure that when you have meetings to understand the patient perspective, you are obtaining a representative sampling of the intended population and methods to collect meaningful patient input, what matters most to them throughout drug development and treatment and methodological considerations for the collection of that data, reporting, the management of that data, and analysis.

The second item here is methods to identify what is most important to patients with respect to disease burden, treatment burden, and benefits.

Accordingly, you can see we progress to measure impacts of those burdens and how to best collect that kind of information in clinical trials, how to analyze that information and incorporate it into clinical

endpoints for decision-making, and what FDA will do with this information.

So under number five, in fact, provide guidance to the public about how they might submit a draft guidance for FDA consideration, so that is a bit of another important area that came up, how can the community help support progress by submitting draft guidance, how to submit this information to the agency, how we would intend to respond, and then how we would use this in supporting our benefit-risk decision-making.

These are all very important components, and I will say that there is a very excellent alignment with where we are going in PDUFA VI commitments as well, per Malcolm's discussion before.

We have a plan on Section 3002 that is required by statute that is nearing completion, and we are integrating the time frames we had planned in PDUFA VI with those that are required in the Cures Act to ensure good alignment.

Thank you.

DR. McLELLAN: Thank you, Dr. Mullin.

DR. BUCKMAN-GARNER: Hi, everyone. Good afternoon. I am ShaAvhree Buckman-Garner. I am the director of the Office of Translational Sciences in CDER. We are a super-office. We house the Office of

Biostatistics, the Office of Clinical Pharmacology, the Office of Computational Science, and the Office of Study Integrity and Surveillance. We also house the biomarker qualification activities for the center in collaboration, of course, with others within the center and within the agency.

So what I want to do is talk to you a little bit about another provision within the act that has to do with advancing drug therapies, specifically focused on drug development tools and the qualification of those tools.

This first slide is really just to show you the magnitude of activities that have been going on in this space since 2006 to try to establish a framework for the development of these types of tools. This timeline really focuses on biomarkers. We are not going to go into detail, but I want to point out that, in 2006, we issued, as a white paper, the critical path opportunities list. There, it focused on the stagnation in the drug development pipeline and specifically indicated that qualification of drug development tools was a key area that we needed to focus on.

Since that time, we have had a variety of guidance documents that have been developed, manuals of policies

and procedures around the qualification effort. We have had collaborations with our European colleagues at the EMA. We have initiated a novel approach with these critical path innovation meetings where we have scientific discussions with scientists from around the country around novel drug development tools. This not only includes biomarkers but clinical outcome assessments, novel technologies, novel tools and approaches.

We also launched a letter of support program. So for biomarkers and drug development tools that are not quite ready for qualification but we want to send a signal to the external scientific community that they need to pay attention and focus on development of these efforts, we have launched that program as well. We have had a variety of meetings and workshops to try to understand the evidentiary criteria for qualification.

We have also issued surveys, both publicly and internally to CDER, to try to understand how biomarkers are being used and how they can best be applied.

So this just gives you a general concept of the amount and volume and variety of activity in the space that we have already launched.

Now let's move to Subtitle B, specifically advancing drug therapies. This is Section 3011 on the

qualification of drug development tools.

As it is written, it applies to primarily biomarkers and clinical outcome assessments. To be clear, the definition indicates that qualification means that a drug development tool and its proposed context of use can be relied upon to have a specific interpretation and application in drug development and regulatory review.

We have been called upon in this section to establish a process for qualification of drug development tools. Be mindful that we already have a process, but now we are refining that process to be in adherence to the act.

It calls upon us to develop guidance that provides a conceptual framework describing appropriate standards and scientific approaches to the development of biomarkers as well as clinical outcome assessments. It calls upon us to develop guidance that helps delineate the qualification process.

We have been asked to hold public meetings to describe and solicit public input regarding the qualification process, to issue a public report on these processes as well as publicly post information on our qualification submission status, so to enhance the transparency around what we have received, what

decisions we have made, and where they are within the process.

So we are excited about this opportunity. We think it is in alignment with over a decade of efforts that we have done in this space, and we think it is a wonderful opportunity to move forward and, hopefully, work collaboratively with our scientific colleagues.

Thank you.

DR. McLELLAN: Thank you so much.

Our last presentation, Dr. Marks?

DR. MARKS: Thank you very much. It is Peter Marks. I am the director for the Center for Biologics, Evaluation and Research, and I am going to tell you about the four regenerative medicine provisions in the Cures Act.

The field of regenerative medicine is a rapidly developing area that involves innovative products, many of which incorporate cutting-edge technologies. In recognition of their promise to address important unmet medical needs, Congress incorporated at least the following four major provisions into the Cures Act, and they represent, as shown on slide 14 here, Sections 3033, 3034, 3035, and 3036.

Section 3033 talked about the accelerated approval for advanced regenerative advanced therapies. I will

tell you more about that in a moment. Section 3034 about some guidance that we need to issue regarding devices used in recovery, isolation, or delivery of regenerative advanced therapies. Section 3035 is really just a straightforward report on submissions that we get in this area of regenerative advanced therapies. And Section 3036, which I will tell you about more, is telling us to go ahead and develop standards, work toward development of standards of regenerative medicine and regenerative advanced therapies.

So the goal here, I am on slide 15 now, of the first provision, Section 3033, it developed a regenerative medicine advanced therapy designation. We have added the word "medicine" into regenerative advanced therapy here. It actually makes it convenient to call it RMAT. The designation program is to help expedite the development and review of regenerative advanced therapies.

We define these as therapies that include cell therapies, tissue engineering products, human cell and tissue products. For the designations, they have to be designed or developed to meet serious or life-threatening diseases or conditions.

And in the process of requesting the designation,

those sponsors interested have to submit preliminary clinical evidence indicating that the drugs have the potential to address an unmet need in that disease or condition. The FDA then has 60 days to get back to the sponsor.

The designation will provide the sponsors with increased interaction with the agency as well as with the opportunity to use a somewhat expanded definition of what is acceptable for fulfilling postapproval commitments.

Then what I would say right now is that we have already worked to get the process in place. It is quite interesting. This was enacted into law on December 13th, 2016. I know the date very well because on December 14th, 2016, we received our first designation request. And on the Web site, there is a process that is in place.

As part of this, though, as you may be aware, the scientific challenges, and I am on slide 16 now, the scientific challenges behind these therapies are significant. Unlike small molecule drugs, which can be characterized often by methods such as HPLC or mass spec quite nicely, even if one could understand the chemical constituents of the cells that are there and in such a manner, one cannot understand the biologic

function in that way.

So one of the key challenges here is trying to facilitate reproducibility in manufacturing. Toward that end, Section 3036 was a direction to work with others. In this case, to coordinate and prioritize the development of standards and consensus definitions of terms in consultation with the National Institute of Standards and Technology and other stakeholders, and to identify opportunities for the development of laboratory regulatory science research to help facilitate the development of these products, and then ultimately incorporate those into guidance issued by the agency.

So we are in the process now of working toward getting these partnerships in place because we very much agree that having development in a collaborative manner of standards that help with the development of these products will facilitate reproducible manufacturing and will hopefully take some of the uncertainty out of product development.

I will stop there. Thanks.

DR. McLELLAN: Thank you, Dr. Marks. That was great.

Before we start in on our process here, are there any general questions regarding the three overview

presentations? They were designed purposely to try to give you a better sense of how the FDA is approaching the overall effort here. This would be a good time just to posit any general ones before we get into specifics.

All right, let's go ahead and proceed. So what we will do at this point, I will ask for a member of the committee to please provide a motion to review the work plan, and I will also seek a second.

So if someone would make that motion to get us going, I would appreciate that.

DR. GOLDMAN: So moved.

DR. McLELLAN: Who is that?

DR. GOLDMAN: Lynn Goldman.

DR. McLELLAN: Thank you, Lynn.

Is there a second among the committee members?

DR. SARWAL: Second.

DR. McLELLAN: Names, please?

DR. SARWAL: This is Dr. Sarwal.

DR. McLELLAN: Thank you.

So we have a motion, and we have a second, so we are open for discussion. This will launch us into our review process.

Again, we are being asked to review the work plan. This is not to authorize or approve the work plan. It

is to review and pass on comments. Nevertheless, it has to be an official action.

So what is our charge? Our charge is to look specifically at the criteria used by FDA to prioritize. So we will be looking at those four points, and then looking at the proposed activities under each subtitle and section.

As you looked at that document, the summary, you will notice that inside each of the sections in the subtitles, they are generally broken up into -- this is the first paragraph describing what the Cures Act calls for, and the second paragraph is often describing FDA's proposed activities. So something just to keep in mind.

You will also probably notice that Subtitle E is missing. That is because Subtitle E, which is Antimicrobial Innovation and Stewardship, is managed currently under other funding and programs and does not have any allocation of funding out of the American Cures Act. So in this case, we will set that aside. It is being dealt with under other programs.

So having said that, the place to start, of course, is the criteria, and we have four major criteria. I am not going to reread these to you, but I will ask you to focus on that.

The first bullet is about fostering innovation and creating integration of advances across all of the programs that we are directly looking at here, all for the purpose of improving the agency's product review sets of tools and processes.

Our second criteria is a focus on the greatest need modernization in the scientific process.

The third criteria is to focus on delivery of services to patients, the medical product industry, academia, and health professionals.

And then the fourth criteria is to look at other funds, which may not be available and, therefore, it is a choice to use these funds to go after these.

So the question is, are these reasonable? And I will take the chair's prerogative to at least start you with a comment. As I have been diving into this to quite some extent, I am feeling very confident that these create a nice criteria to work against. They certainly appear reasonable.

But I am very interested in other comments or suggestions that the committee may have regarding this. I will open the floor. Please identify yourself first, and then I will recognize you, and we will proceed with your comments.

DR. GOLDMAN: Lynn Goldman.

DR. McLELLAN: Lynn, go ahead.

DR. GOLDMAN: Hi. So thank you so much, Mark. I have to agree with you that, in general, these are very reasonable, and I think that they are very much in parallel with the act. And actually, I congratulate the FDA for having been able to get as far as they have gotten with such a short period of time.

There is one area that I feel is embedded in the mission of the FDA, and in fact somebody, I think Malcolm alluded to this right at the outset, and that is that FDA is a public health agency. And one thing that I feel is not explicit in the criteria that I would like to see brought out somehow is the issue of public health.

I think there are a lot of different ways that could come about. For example, on slide number eight, which is where the criteria are, the idea of the most immediate impact on the delivery of services, but it is really the most immediate impact or perhaps one might consider the breadth of the impact but also whether the impact, the number of people that are impacted, the extent to which the new product moves toward prevention, addresses disparities in health, perhaps lowers cost of treatment, perhaps increases the efficacy, but also perhaps addresses priority of public

health concerns that cause a lot of morbidity and mortality, whether it is perhaps drug addiction and opioids, or the impacts of high blood pressure and diabetes, things that have broader impacts, or perhaps moving upstream to prevent cancer, new products that perhaps are chemo preventative that might for many, many, many people in the population help to prevent cancer.

I am saying this while understanding that explicitly the statute does not say that. However, I think that the mission of the FDA does say that. And I think that Congress may well have expected that FDA would have some consideration about public health integration, so I am putting this forward as something to think about.

Thank you.

DR. McLELLAN: Great point, Lynn. I think you have made a good case on that.

On any of your comments, let me mention to Malcolm and all of our presenters as well as the other supporting individuals from FDA, I always welcome you to either react to or not. In general, if we are not hearing from you, we will assume that the comment being made is within a degree of reason and will be considered as editing moves forward.

MR. BERTONI: Thank you, Mark. This is Malcolm Bertoni. We appreciate that invitation.

My own comment on Dr. Goldman's suggestion is thank you very much. What do they say? Sometimes fish don't talk about the water because they are swimming in it all the time. I think there are things where perhaps we don't recognize, and it takes another pair of fresh eyes to state something that probably should be, so we will certainly take that back and give that full consideration.

DR. GOLDMAN: I will say, Malcolm, that I typically come up with the most obvious points, but thank you for saying that.

DR. McLELLAN: Thank you, Malcolm.

Are there other comments regarding the criteria? I am separating this from our follow-on work, because I feel it is fairly important that we be in a common place here regarding the criteria.

DR. JENKINS: Annalisa Jenkins.

DR. McLELLAN: Annalisa?

DR. JENKINS: Yes, again, building upon Lynn's commentary, I would also individually like to compliment the agency on a very broad, comprehensive, and thoughtful document.

My comment relates again to bullet point three,

and I guess is in a similar vein. But I would like to see the notion of safe and appropriate use for medical products come through. It is a little bit unclear in terms of the delivery of services comments. The delivery of services is a little bit vague. I would ask the agency to perhaps be a little bit more focused.

There has been a lot of debate around the Cures Act. Ultimately, I believe the intent was to ensure the ability of medical products most likely to make the most impact on the health of the public. This act would encourage, enable, and accelerate the delivery of those in a safe and appropriate manner.

So again, not wishing to wordsmith. I know this is difficult by committee. I just believe, again, that Congress -- and those, actually, that really supported this act and charted it through -- might want to see slightly more focus on those two areas.

Thank you.

DR. McLELLAN: Thank you, Annalisa.

Are there other comments on these criteria?

DR. AFSHARI: Yes, Mark. This is Cindy Afshari.

DR. McLELLAN: Cindy?

DR. AFSHARI: I just had a comment. I wanted to reiterate the feedback, the thoughts that went into this. They really are on short order to provide a very

thoughtful response to how the agency would move forward with this act.

I just wanted to bring a comment briefly forward on the first bullet. Really, the focus here is on innovation, and there is a continuing challenge that the speed and the treadmill speed I guess is going up with respect to some of the technical and technological advances that are truly innovative.

So we heard comments that the agency would, on a yearly basis, reevaluate objectives and really make sure that they are centered, and the appropriate focus on innovation is there. I would say that you should give some thought to the mechanisms where the agency could look to really ground that opinion. There are going to be a lot of things coming out that really are not going to be ripe for the investment of the agency, but we also want to make sure that the really emerging technologies are not ignored.

So I think the devil is in the details on this one, but we want to make sure that there is a sustainable plan there with respect to ensuring that resources are truly directed at the most innovative approaches that will bring the highest value back to patients and the agency.

DR. McLELLAN: Very good. Thank you, Cynthia.

Any other further comments regarding criteria?

Good, let's go ahead and move on. We will now go into the actual proposed work and the work plan. So if you are following in the original document that was sent to you, we are at the bottom of page 4.

Let me propose that, as we go through this, we will keep a pretty good pace. In other words, I will be identifying the subtitle and, indeed, the section, when we get into enough details in the sections, and point to the essence, at least as I perceive it, of that section, and then call for comment. We will use the same approach where we will ask each individual to feel free to speak up, identify yourself. Again, we would also welcome FDA staff to react to each of the comments.

So our first one is Subtitle A focused on drug development. You will note that there are three key parts here focusing on patient experience data, looking at acceptable methods, and then directing FDA to issue appropriate reports focusing on the development tools that will be used.

So let me throw this open for any comments from the committee members regarding the appropriateness and design of this section.

DR. REISS: Ted Reiss, can I --

DR. McLELLAN: Yes, go ahead.

DR. REISS: May I make a general comment?

DR. McLELLAN: Yes.

DR. REISS: Okay. I just want to make a general observation, if I could, sort of about the overall work plan, which I think is, also to echo everybody else's thoughts, is excellent, right on the money, and sort of appropriate to the limitations that the agency has in terms of funding and allocation, and so on.

I just wanted to make the comment that what struck me was, in many of the different sections, a lot of the focus is on guidance development, and appropriately so. You have to start somewhere with specific criteria about how to move the area forward and have review criteria.

But I was looking for in the work plan just a little bit more about the link perhaps in these various different areas about helping to generate some new knowledge rather than just criteria by collaborative efforts or use of some of the mechanisms that may be available to the agency, the CERSI program and so on and so forth. I was just wondering if there was a strategy sort of involving, in putting this work plan together, whether anything like that was possible or entered into the agency's thinking in coming up with a

plan.

Thank you.

DR. McLELLAN: Thank you, Ted.

I think that would call for probably a reaction. Malcolm, maybe you can identify someone to step into that conversation.

DR. MULLIN: Hi, Dr. Reiss, and others. This is Theresa Mullin. I will try. Just speaking for one section, I think I can offer some of the kinds of considerations, and I will look to my colleagues to add more.

I think that you are absolutely correct. I think that, in our view, I would say the discussions in the center and the agency, there are a lot of, let's just say not only innovative methods to use in drug development but a lot of -- these are innovative. And I think it means that they are new. It means that they introduce uncertainty, if you will. They introduce regulatory uncertainty, as well as they introduce scientific uncertainty, in some cases.

And there is regulatory uncertainty. And how will the regulator handle it when I submit something? Is this going to be an acceptable format?

We might not even get submissions. We might fail to even go forward with these, if there is not enough

assurance or sense on the part of outside stakeholders, including researchers, those working in collaboration perhaps with drug developers, to go there, to use innovative trial designs, or to submit patient-provided information and experience information. So guidance is a key element.

To your point -- and actually the time frame, for example, under Section 3002, which I am most familiar with, indicates eight rather challenging areas that are all critically important to the success of integrating the patient's voice in drug development. But there is a lot.

So what we have tried to do is break that down into a series of guidances that are logically related in many cases but are manageable chunks, if you will, of the work. And we propose -- and this plan that will be out pretty soon. It is also due by mid-June, to be available.

It shows exactly how, in these cases, we are going to begin with a public workshop to have outside stakeholders, researchers, patient community sponsors, and others who have a lot of experience in these areas, come and share with us what they would recommend, what methods they consider, what tools are available, so we have the benefit of that information as we go into

developing a first draft of the guidance.

The statute also requires that we produce a final draft within 18 months of the close of the comment period. And the work that I have just described, these eight areas, should be completed within 5 years of enactment. So we have, at least in the case of 3002, time considerations. I think we certainly anticipate making use of the resources of outside organizations, including CERSI, which may require some additional advanced planning, but we are doing that as we get into the Patient Voice.

But I think where we have statutory requirements for producing the guidance, we probably plan the activities to be sure to meet that requirement, but as you say, try to engage the other stakeholders in the community as much as possible to benefit from that along the way.

I will stop there and ask others if they have things to share.

I am seeing some heads nodding, that what I said is okay.

DR. McLELLAN: Thank you, Dr. Mullin.

DR. REISS: Thank you.

DR. BUCKMAN-GARNER: I completely agree, Theresa. This is ShaAvhree Buckman-Garner.

DR. McLELLAN: Please remember to identify yourself.

DR. BUCKMAN-GARNER: I did at the beginning, but I was speaking quickly. This is ShaAvhree Buckman-Garner. I am the director of OTS.

I just wanted to reiterate that also in the drug development tools implementation space, we do and have engaged with the CERSIs in some of the workshops that we have had to understand evidentiary criteria. We have done this with the Maryland CERSI.

We also have in the statute laid out that we have to be able to engage external experts. So I anticipate that that will include CERSI consortia, public-private partnerships, a variety of different types of experts.

DR. McLELLAN: Very good. Thank you.

Ted, thank you for your comment. We certainly appreciate the focus on wanting a little bit more than just criteria. But as you indicate, you have to start somewhere.

Any other comments regarding Subtitle A, patient-focused drug development, before we start into drug therapies?

DR. BAHINSKI: This is Tony Bahinski, Mark.

DR. McLELLAN: Tony, go ahead.

DR. BAHINSKI: Just a quick one. Under the

subheading here down below, I am actually heartened to see that part of the funds will be used to strengthen the staff with clinical, statistical, psychometric, and health outcomes research experience within the FDA.

I see that as something that can be broadly applicable to a lot of the areas that are included in the work plan, particular areas like modern trial design and evidence development. So I think that is a key to making this a success.

DR. McLELLAN: Excellent.

DR. GOLDMAN: Lynn Goldman. I have a comment.

DR. McLELLAN: Yes, Lynn?

DR. GOLDMAN: I think that in this area of patient-focused drug development that, one, a really great thing is that, under PDUFA, that the FDA already has initiated a lot of kind of work and that there is a solid base upon which to build, on the upside.

What I worry about, and it connects somehow to that last comment, and that is whether the FDA actually has methodology for obtaining generalizable data from these processes, because at least in what was written in the report, I certainly get an impression of certainly a lot of collection of anecdotal information and information from people who will show up at a meeting, but is that generalizable data that is

reflective of the population of patients with a specific disease?

And whether or not it is generalizable, it is not certain at all how these reports actually used in drug regulation, and whether there are other -- so I think there is the science of doing a qualitative collection of data. You bring people together and you interview them. But there needs to be quantitative assessment of what is going on, as well as qualitative assessments.

And then some sense that there is some kind of risk science being employed to say, all right, then how do we actually factor this into regulatory decision-making? You know, the loudest voices are heard and then the agency believes that that is reflective of what is needed, which I am sure is not at all what is contemplated, but it was not actually coming through to me for that.

DR. McLELLAN: Thank you.

DR. MARKS: This is Peter Marks.

DR. McLELLAN: Go ahead, Peter.

DR. MARKS: Thanks for that question.

The agency is actually quite aware of this. We have statisticians in each of the medical products centers, as well as others, who are very interested in the science of converting the qualitative information

that we receive into a more quantitative or a more representative viewpoint that can be incorporated.

I think all of the questions are not yet answered, but the major point is well-taken, that we need to work and we are working to be able to turn the information we get from patients into something that we can have some confidence in as being reflective of a more general patient population, because we do understand that, yes, the loudest voices tend to get heard.

But there are ways to try to make sure that what we get is representative. And the statisticians are working on that.

That goes over not just into these patient-focused drug development meetings but also into the whole concept of patient-focused drug development and feedback that one could get as products are developed.

So I think your point is well-taken. Although I cannot tell you that we have answered every question, I think we are working in that direction.

I think Theresa Mullin wants to say a little bit more about that.

DR. GOLDMAN: Theresa, before you add, in connection to what Peter just said, there is a lot of discussion in there about having to deal with the RIBs, but not so much with the HIPAA and data-sharing issues

that I think are going to be very important as you actually unfold your work plan, in terms of being able to get a broader data.

But anyway, go ahead. I am sorry.

DR. MULLIN: Okay. Thank you for that.

Maybe this is partly that I went so quickly, to keep within my allotted time. I am able to spend hours talking about this topic, so it was with great self-control that I limited myself to probably more than 5 minutes.

So what you are hitting on is exactly I think one of our key findings from what we have been doing. I think the meetings that we have been conducting have been -- I do not want to say surprisingly powerful and impactful, but I think they have been just because the perspective of the patient has been, in some cases, offering new insight to our very experienced clinicians and reviewers who have worked in this area for some time, information not necessarily in the literature.

But as you say, these are qualitative sections, not to disparage qualitative information, but we are telling people an important place to start. But if you were to look at the posted proposed commitments for PDUFA VI, which are available on the Internet and our Web site, you will see that, in fact, this kind of

thinking is just where we are headed, just as you are describing.

How do we go from this powerful but qualitative meeting to a series of steps that are really needed to, first of all, make sure that we are capturing a fully representative cross-section of the patients with a disease, not just those who make it to White Oak or to a nice, wealthy suburb focus group location, and so on? So how do you do that to really have methods to collect what is most important and meaningful to patients? So what are the variety of methods one might want to use?

And then how do you step-by-step go about methodologically testing and trying to translate that into a set of measures that can include it as a questionnaire or a survey instrument in clinical trials, addressed by everybody, that could have about as good a quality as any of the other information collected in those trials, because that is really what we want to have, if we are going to be making decisions. We really do want that more vigorous information, to be able to use it for very much -- and for broader use in regulatory decision-making.

So that is a lot of work, a lot of steps. So we did parse it out into a series of guidance work, a series of workshops, and so on, to get to those very

important considerations that you are raising here, and I think we fully agree.

We note the concern about HIPAA. Much of this may be done as part of clinical trial data collection.

Thank you.

DR. McLELLAN: Thank you, Theresa.

And thank you, Lynn, for the comment.

I will throw one quick one in too, Peter, and that is, as those statisticians are working through that analysis of evaluating qualitative work and moving into the quantitative range, that could be quite pioneering, and it would be of significant importance, certainly in the academic community, to hear about that work and see that work published as much as possible. So thank you.

Any other comments to this section?

DR. BAHINSKI: Mark, this is Tony again. One quick follow-up?

DR. McLELLAN: Go ahead, Tony.

DR. BAHINSKI: I think there might be some learning here from things like the citizen science initiative from the EPA. There might be some good links there on how to train people to gather good data and turning that qualitative into more quantitative data, so you could almost start like a patient science or patient scientist initiative.

DR. McLELLAN: Good point. Yes, absolutely.

We have completed one. We have 19 more of these sections, so we want to keep a bit of a pace here.

Let's go ahead and move on to Subtitle B. We will be talking about new drug therapies. Our first section here is qualification of drug development tools. These will be a little bit more targeted than our first one here and may enable us to move forward a little bit faster.

This section calls for a qualification process regarding drug development tools, and I guess most importantly asks FDA to establish evidentiary criteria that might be used.

So I will throw this open for comment to members.

Okay, hearing none, I will assume that we are in reasonable agreement regarding the plan there.

Our next section is Section 3012 talking about targeted drugs for rare disease. It focuses on development, review, and approval of genetically targeted drugs and protein-targeted drugs.

Any comments regarding this section?

All right, I did not mean to scare you all off. Feel free to give a comment.

DR. TOSI: This is Laura Tosi. This is probably the wrong place for it.

DR. McLELLAN: Go ahead, Laura.

DR. TOSI: I am a pediatric orthopedic surgeon, and I do a lot of work with rare disease kids of various stripes. I do not think it is within the context of this work plan, but I hope it will come up somewhere.

What we are seeing is that rare disease drugs have really become the new, exciting, go-go marketplace, and some of the prices that are being charged are mind-boggling, and so many kids are going to be denied.

Is there anything under this to try to increase competition between the drugmakers? And what statutory authority is there to sort of say, guys, you cannot go crazy with this?

DR. McLELLAN: Thank you, Laura.

Is there a comment from FDA staff?

DR. MARKS: This is Peter Marks. Your point is well-taken. Unfortunately, FDA approves products and we do not take the price or the potential price of them into account. Granted, the way we generally try to address those issues is by making sure the marketplace is still -- there are many potential drugs that could help people, because then hopefully the marketplace, natural competition takes care of that. But we do not have statutory authority to regulate the price of drugs

in that way.

DR. MULLIN: This is Theresa Mullin. I am not an expert in this area, but I can assure you that while there are a number of statutory provisions that already exist to encourage the development of orphan new drugs, there is an additional orphan exclusivity. I think it might be 7 years of exclusivity that they get.

We have done an analysis to look at the clinical trial. The clinical development period is typically shorter, of course, for rare disease drugs. But that exclusivity -- and they typically receive some kind of expedited status when we review them because they are so important. They are typically filling a need that is unmet, a critical need.

So I think there are provisions in place. They may not necessarily produce more -- competition, but I do think that there is a lot of encouragement for the development, but I guess it would be -- but as Dr. Marks says, we do not have authority over the pricing of products, and there have been quite a few developed and to be developed in response to need and perhaps the treatment that is given to help move them along. Almost a third of new approvals in recent years have been for orphan drugs.

DR. TOSI: Yes, that is what we have seen, and it

is very exciting. But it has created, I would argue, the entry of people into the marketplace who do not give a darn about our patients. I am just wondering whether there are any statutes or other things that could be recommended over time that would maybe reduce the financial incentives just a little bit and sort of clean up the act of the people who are getting involved.

That is my political comment, and my frustration comment. I will be quiet now.

DR. RAO: This is Gayatri Rao. I am the director for the Office of Orphan Products Development. If I could just add to the comments that Peter Marks and Theresa --

DR. McLELLAN: Yes, go ahead.

DR. RAO: -- provided already, to echo, yes, certainly, we do not get into the discussion of price. When we do think about incentives, however, in terms of implementing the statutory incentives and in the regulatory framework in which the agency is created, we certainly try to balance ensuring appropriate incentives for new and innovative products with ensuring access to products.

So when you look at things like orphan exclusivity, which was just raised, which provides 7

years of exclusivity, that really gets at the incentive piece, that exclusivity is really limited to just that specific orphan indication, for example. So it would not prevent generics from coming on market that do not have that orphan-protected indication.

So without really going into too much detail, it is just an example of how the statutory and regulatory framework is really set up to try to balance incentives and access.

DR. McLELLAN: Thank you.

Let's go ahead on to our next section. We will move to Section 3013 talking about rare pediatric diseases. This section extends the voucher program for sponsors and essentially asks FDA staff to develop both draft and final guidance for review of rare pediatric disease designations in terms of treatments.

Any comments on this section?

DR. STEELE: Mark, this is Scott Steele. A couple quick questions on the voucher program.

DR. McLELLAN: Go ahead.

DR. STEELE: I believe there was a prior GAO review of the program. I was just curious if there were any proposed actions from that.

And then the other question was, I think it is somewhere else in the Cures Act, but I believe there is

a proposal to create a third voucher program to incentivize drugs targeted at agents that are considered national security threats. I was wondering if FDA is required to put out guidance related to that, if that falls under this, or if that is handled separately.

DR. McLELLAN: Thank you, Scott.

Comment from FDA?

DR. RAO: This is Gayatri Rao. Again, I am with the Office of Orphan Products. I can try to address one piece of this, which is with respect to your question about the first GAO report that came out, and that was mandated --

MR. RAGHUWANSHI: We are getting a lot of feedback. I am going to remind folks on the webcast, or members, to mute their phones when they are not speaking, and also to turn off your computer speakers.

Thank you.

DR. GOLDMAN: If I may comment? This is Lynn. I hear everybody clearly except the FDA staff. I am wondering if that is a speakerphone and they need to be closer to it when they are speaking. It is just a thought.

MR. RAGHUWANSHI: Yes, I heard from our AV folks too. Those of you around the table, make sure you are

at least this close to the microphone when speaking.

Lynn, can you hear me clearly?

DR. GOLDMAN: I hear you perfectly.

MR. RAGHUWANSHI: Okay, it looks like that does the trick.

DR. RAO: Hi, this is Gayatri Rao again. Please let me know if you are having trouble hearing me. I am about as close to the mike as I think I can get.

With respect to the question on the first GAO report that was mandated under the first iteration of the rare pediatric disease prior to review voucher review program, that report was issued on time and essentially said that it was too early to really gauge the effectiveness of the program to serve as an incentive for treatments for rare pediatric diseases.

So when this program was reauthorized last year at the end of September, it is worth noting that as part of that, there was an additional request for a subsequent GAO report in a few years to, again, sort of determine the effectiveness, again, of this program.

With respect to your second question I am going to --

MS. DuPONT: Hi, this is Jarilyn DuPont. I am with the Office of Policy.

With respect to the second question, there is a

provision, 3086, that does talk about innovation exclusivity for national security threats, but that is not included within the eligible innovation funds, but it is being addressed by FDA.

DR. STEELE: Thank you. Part of my question was, if I recall right, the first review highlighted some of the personnel time impacts of the current programs, so I was just wondering with the addition of an additional one, if you were concerned about that.

Thank you.

DR. McLELLAN: Very good.

Any further comments?

In that case, let's move on to Section 3016, grants for studying continuous manufacturing. This is a focus on movement from batch technology into continuous process systems. The FDA has suggested we will issue grants to enhance the knowledge of novel continuous processing technologies.

Any comments from the committee?

Hearing none, we will move on to Subtitle C. We will be focusing on trial design and evidence development.

Section 3021 focuses on unique and novel clinical trial design where FDA would be holding public meetings to discuss and look at new designs and issue guidance.

Any comments from the committee on this section?

Hearing none, let's move on to Section 3022, real-world evidence. The act asks FDA to establish a program to evaluate the potential use of real-world evidence. I suppose that is contrary to fake-world evidence. Sorry. Anyway, looking at data from sources other than randomized clinical designs.

Any comments from the committee?

DR. REISS: Ted Reiss here.

DR. McLELLAN: Go ahead, Ted.

DR. REISS: So I think this is going to be one of the more challenging sections for the agency, but I do just want to raise the issue about nomenclature and what is being excluded here seemingly by the first or the second sentence, and how at least in some public statements that Rob Califf made sort of included the concept of real-world evidence into randomized effectiveness trials.

So that seems to be excluded in this paragraph, but will that be given some consideration or is that being specifically excluded, again knowing that the agency used the term "effectiveness trials" or "effectiveness" in certain ways but used in this context?

DR. McLELLAN: If we can go to the FDA for a

comment on that?

DR. CORRIGAN-CURAY: Yes, this is Jacqueline Corrigan-Curay. I am with the Office of Medical Policy.

In looking at this provision, the provision does specifically ask us to look at data that would come outside of randomized clinical trials. But I also think that we need to look at this as a totality, because certainly, the same data that might be used, real-world data, in a sense, is usually thought about data that is coming from the health care system, claims data -- other sources of data that would probably -- could be used in both settings, and its use in both settings would be informative.

So but certainly, we have a mandate with the language in front of us to also look outside the program --

DR. YASZEMSKI: Hello, Mike Yaszemski here. May I add a comment to that? Hello?

DR. McLELLAN: Go ahead, Mike.

DR. YASZEMSKI: Thank you.

I am an orthopedist, and in our specialty, we have I think one example where this "real-world data" might have played a part. I want to briefly say it. I will not mention the product name, but this is something for

our children with scoliosis.

This was begun -- it took 19 years to get this particular thing through the FDA. This was started for something called thoracic insufficiency syndrome, which is a combination of scoliosis and lung underdevelopment because of reduced chest cage volume.

Something was tried that at least kept some of these kiddies alive, and 8 years into the process, the team at FDA changed, and the new team said that there was not a nontreatment control group. It took a while to say that we started this because 100 percent of these children die. Some of them are alive now. Can we please use the fact that some of them are alive to say that we do not need a control group?

Now that is an extreme example, but I would argue that we should at least have this possibility on the table so that if something comes up where folks would think it is reasonable to proceed without a randomized control trial, that the FDA has the opportunity to have that option open to them. That is all I will say on that.

DR. MOSCICKI: Yes, this is Rich Moscicki. I am the deputy center director for CDER.

DR. McLELLAN: Go ahead, Rich.

DR. MOSCICKI: Yes, thank you.

We do, as a matter of fact, we use, often, single-arm clinical trials in oncology, where we see a large treatment effect and a difference. We recently held a workshop to carefully look at how to borrow other data, particularly for rare diseases where the numbers of patients available are quite small. That might fit somewhat into the category that you just outlined.

Furthermore, we have looked at how to use natural history control groups and what kind of statistical methodology would be optimal. We have approved several products recently using natural history control groups as well in order to do that. So that is an important part of how we would plan to move forward.

Where we see real-world evidence, I think if you look at the article that was published using a number of FDA personnel, including Rob Califf and Janet Woodcock and others, recently in the New England Journal of Medicine, I think it outlines not only some of the issues of using real-world evidence in regulatory decisions, but I think most importantly it says that the world of clinical trials and randomization does not necessarily have to be separate from using real-world evidence.

I think that may be one of the things Jacqueline was trying to also say, that we see where we can do

randomized trials using real-world data as opposed to the more formal clinical trial kind of approach. We also see this as an important way to potentially to postmarketing collection of evidence that supports things like accelerated approvals.

DR. GOLDMAN: Hi, this is Lynn Goldman.

DR. McLELLAN: Go ahead.

DR. GOLDMAN: I mean, I think this is a very important issue not only in terms of the issue of what is real-world evidence. It just seemed to me that they did not mean clinical trials as being the real world, but the ability to use various kinds of health services data to help FDA with decision-making.

So my experience in regulating came from EPA where we never have clinical trials. It is almost never okay to do randomized trials exposing people to things like lead and pollutants and stuff, right? So we are all the time having to use real-world evidence.

And it can be extremely useful in terms of doing things like identifying biomarkers and supportive information that is maybe not routinely collected in trials but might be collected clinically or in other studies that helps you to understand what is going on, and maybe even contribute to systematic reviews and so forth.

So I think this is very important. And at the same time, like I said before about the earlier issues, I do think, in terms of the rest of the HHS, we do have some issues essentially with HIPAA and data-sharing and better access to data, number one.

But also, number two, you do have some opportunities. And I am surprised it was not mentioned that there are a number of efforts already at FDA to collect -- data usually for post-market surveillance. Maybe you can use leverage off of some of that data to get some of this information, obviously -- you need a lot of data.

But I know that they are using Medicare databases and Medicaid databases in some of the programs, Kaiser Permanente, that kind of thing. You might already have some data that FDA could use for this.

DR. McLELLAN: Thank you, Lynn.

Let's go ahead and move on to our next section.

That is Section 3023, protection of human research subjects. This section calls for FDA to harmonize, if you would, their regulations to the HHS common rule, which oversees human subject regulations.

I will throw a personal comment in here. As chair overseeing teams of researchers, this is an important statement, and I was certainly pleased to see this. We

encourage that these steps be taken such that the common rule is implemented to the maximum possible.

Other comments regarding the section?

Hearing none, let's go on to the next section, Section 3024. This is the informed consent waiver for clinical investigation. This focuses heavily on the Institutional Review Board and its role in terms of approving risk. It also talks about, I believe, the centralization efforts in this.

Let's throw this open for comment to the committee.

Okay, not hearing too much here. Let me throw a personal comment in then. I guess I am always concerned, if I am divvying up responsibilities, I find centralized IRB to be conceptually a great approach but often the centralized institution wishes to decentralize the risk and often will pass back risk to other partnering institutions. I guess what I am saying is it is not always crystal clear as to how well this can be implemented.

DR. GOLDMAN: This is Lynn. Hi, again. I just think that we are all right now trying to implement the revised common rule, which was recently finalized by HHS. That does have provisions around that actually, and I do not think -- we are not in a position yet

where I can say we have all the answers about how to do that or even how we are going to staff it in terms of all the communication challenges and so forth, so anyway.

DR. McLELLAN: Thank you, Lynn. I believe that reflects many, many institutions that I have spoken to regarding this also.

Any further comments?

DR. XIE: Hi, this is Sean. Hello?

DR. McLELLAN: Go ahead, Sean.

DR. XIE: I had a question. I could not figure out how to get in.

So this question, even FDA, if you waive those regulations or the provision of IRB -- its own regulation will require to have to file IRB in order to access all of the clinical data. Like at my center, access to the clinical drug abuse or Alzheimer, the clinical data, that is required. So that means that if FDA waives its right, then the university does not have to file those? We can easily access the data collected by FDA? Is that right?

DR. McLELLAN: Would FDA staff like to comment?

MS. DuPONT: This is Jarilyn DuPont, the Office of Policy. I am not quite sure we understand the question.

DR. XIE: Okay, let me rephrase it, because on FDA's side, when you waive those IRB requirements, right? That's the --

DR. McLELLAN: I believe you are forced to waive the informed consent.

DR. GOLDMAN: If I may, I think I understand what he is saying, which is that institutions have IRBs that impose requirements. If the FDA is waiving informed consent, does that override the institutional IRBs and their requirements or will there still be the ability for the institutions to impose their own requirements?

DR. XIE: That is right. Exactly.

DR. LESS: Hello, this is Joanne Less, director of the Office of Good Clinical Practice at FDA.

I think there is some confusion over what this provision is. This is actually giving FDA the same authority that all of the common rule agencies have for the IRB to waive informed consent, so this is not FDA waiving consent. This is the same authority that you have under the common rule under Section 116(d).

So if an investigator wants to go back into 10,000 medical records to look up some data, it would not normally be considered feasible to do that kind of study. They can go to the IRB, and the IRB can say you do not need to get consent under that type of

circumstance.

DR. XIE: Okay.

DR. GOLDMAN: I see. So the investigator is doing a study that the FDA might review, and if the investigator's institution is willing to waive it, then the FDA will accept that waiver, is what you are saying.

DR. LESS: Exactly. This is all up to the IRB to decide that it is a minimum risk investigation. It is not violating the patient's rights, safety, welfare. There is no other way to do the study without this waiver. Then we would be able to accept the data.

Right now, those studies cannot happen, so even though that waiver can happen for common-rule studies or federally funded studies, those kinds of studies cannot be done under FDA regulations.

DR. GOLDMAN: Or could not be utilized by the FDA to make a regulatory decision. FDA would not be able to fund it or would not be able to use it?

DR. LESS: We would not be able to use that data. That is correct. Or fund it. Right.

So it is just giving us the same authority that all the other common-rule agencies have had for decades. It is another piece of the harmonization of our regulations with the comment rule that is covered

under the previous section.

DR. McLELLAN: This is Mark. Let me suggest then, Malcolm, that this might need just a little bit of tweaking in terms of the wording here to clarify that because I did not read it to that understanding either. I think, however, with some wordsmithing here, you could get that to better clarity.

MR. BERTONI: Thank you very much. We will take a good look at that.

DR. GOLDMAN: May I ask a follow-up question on that?

DR. McLELLAN: Go ahead, Lynn.

DR. GOLDMAN: Is there some kind of a guardrail on that? I am just thinking about studies that might be conducted in other countries, I mean where perhaps the IRB processes might not be as stringent, to make sure that the waiver, the granting of the waiver, was done within an appropriate deliberative process under the common rule?

I mean, I think that has always been something that has been positive about the FDA policy, that it has not been all that easy to just go out and do unregulated studies in other countries and bring the data in for approval in the U.S.

DR. LESS: Again, this is Joanne Less, from the

Office of Good Clinical Practice at FDA.

These would be studies that are under FDA's jurisdiction. So if they were doing them in the United States, they would follow our requirements under Part 50 for informed consent, and then the IRB could waive informed consent. If they were being done outside the U.S., it would depend on whether or not the study was under an IND. Then they would be expected to follow Part 50 and waiver could occur.

But it would depend on the local laws as well. So some countries that would not permit that, then they would not be able to use the waiver. If the local laws and regulations permit it, then they could use that waiver.

DR. McLELLAN: Additional comments?

Hearing none, let's go ahead and move to our next subtitle, Subtitle D, patient access to therapies and information.

Our first section is Section 3031, summary level reviews, which directs the FDA to essentially develop policies and procedures for use of summary level data as appropriate for oncology application.

Comments to this section from the committee?

DR. JENKINS: Annalisa Jenkins.

DR. McLELLAN: Annalisa, go ahead.

DR. JENKINS: Yes, just a question, actually, for clarification. I noted across the work plan that, of course, oncology features highly, not surprising given the need here. I just wondered whether within this, and I think later in the document when we get on to Subtitle G, consideration is being given to apply some of the best practices that have already been achieved in the oncology space to certain other of the divisions that also present more immediate public health concerns and actually particularly in areas of degenerative brain disorders where there has been a real challenge in making progress in scientific and medical innovation.

DR. McLELLAN: Is there comment from FDA?

Not hearing any comments, so --

DR. KIM: This is Tamy Kim, the associate director, regulatory affairs, for Oncology Center of Excellence.

So far in OHOP, we have completed about three or four separate level reviews. We have developed certain policies and procedures within OHOP and OCD. We have presented them to the Medical Policy Committee. We can certainly do that again in a more formal manner.

DR. JENKINS: Thank you very much.

DR. McLELLAN: Thank you. Appreciate that.

Any further comments?

Hearing none, let's go to Section 3033, accelerated approval for regenerative advanced therapies where we are looking at FDA building on current programs to extend and expedite programs available for regenerative medicine. We heard extensively from FDA in their briefing on this.

Any further comments from the committee regarding this section?

Hearing none, let's go to Section 3036, standards for regenerative medicine and advanced therapies. It essentially drives establishment of standards and consensus definitions for regenerative medicine therapies and pushes FDA or establishes FDA as going after this process.

Are there comments and suggestions for this section?

DR. BAHINSKI: This is Tony Bahinski.

DR. McLELLAN: Tony, go ahead.

DR. BAHINSKI: I think the quality control and the good manufacturing processes here are a big need, and I am glad to see they are being focused here.

Just outside of the remit of this group but I think similar processes need to be applied to quality control for preclinical cell sources for use in

preclinical research. There is a big gap there also, especially in iPS drive cells.

DR. McLELLAN: Good comment. Thank you.

Any further comments on this section?

Hearing none, let's go to Section 3038, combination product innovation. This section pushes FDA to modernize regulation of combination products. It mandates that FDA develop, publish, and maintain a list of efficiencies for complying with GMPs in these types of products.

Any comments to this section from the committee, please?

DR. REISS: This is Ted Reiss again.

DR. McLELLAN: Go ahead, Ted.

DR. REISS: Hi, as I was reading this, I was a little confused about what the overall goal of this section was. Does this just have to do with manufacturing? Does this have to do with simplifying and making it easier to do combination products and chemical entities together? Does it have to do with a new chemical entity and a device that may go along with it? Or all of the above, or some subpart thereof? So any comment on that?

MR. WEINER: This Barr Weiner, associate director for policy for Office of Combination Products at FDA.

This short answer is all of the above. It is a pretty comprehensive sweep in this section regarding premarket and postmarket considerations for regulation of combination products. And our basic proposal is to try to ensure that that is sufficient and consistent and coordinated by the agency. And the listing provision that was referenced earlier goes to efficiencies for compliance with CGMP for all combination products and what options there might be for achieving that.

DR. XIE: Hi, this is Sean Xie from the University of Pittsburgh.

DR. McLELLAN: Go ahead, Sean.

DR. XIE: Maybe we should divide it into two categories. One is the postmarket drug, those that have been already approved by the FDA. It is in the market. So those drugs for treating, many of those are already in the clinic for combination therapy. But if it is a proposed new drug protocol or combination, then maybe the approval processing may be different, right?

MR. WEINER: The way combination products are regulated by FDA, they are regulated under some sort of application type that exists for the constituent parts that they are composed of, so drug pathways, drug device pathways, or biologic pathways. We usually pick

a pathway based upon the constituent part that provides the primary mode of action for the combination product.

But there is no special application type. So the application just depends upon usually the center that has lead.

In terms of data requirements and requirements in general, if the products are already approved, then combined, the issues would be focusing on the new questions relating to the new combination of the two products. That is one of the issues that the proposed legislation calls upon the agency to focus on, in order to approach.

Does that answer the question?

DR. XIE: Well, let me just clarify my question. So let's say there are two drugs interdicted. Acting on two pathways, they may create synergy used in combination. So then in this case -- getting to basically clinical trial right away, right? As long as the dosage is not exceeding the approved dosage.

MR. WEINER: So just to clarify the definition of combination product under FDA's regulations, it is when you are combining two different types of medical products, two or more. So it is a drug and a device or a biologic and a drug, or all three together, for example. So if you are just combining two drugs, we

have regulatory authorities for questions to address in combination therapies and making sure there is improvement in therapy to take account of the risks.

But that is a separate paradigm that is not really part of the combination products regulatory program.

DR. XIE: Okay. Got it. Thank you.

DR. McLELLAN: Thank you, Sean.

Any further comments?

Hearing none, let's go to Subtitle F. We will be focusing on medical device information and focus first under Section 3051 on the breakthrough devices, which essentially expands FDA's expedited access pathway program to move devices quickly to market. The action planned here, that there will be an accommodation of increased workload to acquire the kinds of systems needed to fully implement this program.

Let me throw this open for comment or questions?

DR. SARWAL: Yes, this is Minnie Sarwal.

DR. McLELLAN: Go ahead, Minnie.

DR. SARWAL: Thank you. I just had a question, actually, maybe a little specific to this but generally for accelerating the pathway overall for medical device innovation.

So I think in this Section 3051, it really talks about increasing the workload within the FDA to really

increase the acceleration of the approval. But I think overall, for the Cures Act, getting the devices more rapidly to market, the easier paths or the cheaper paths is actually very critical.

So perhaps I could request the FDA -- we talked about really large clinical trials versus smaller studies, real-world evidence, et cetera. Would there be overall a plan to really simplify the requirements of some of these pathways to really get medical devices not just that are helping life-threatening conditions but really I think that are very important for a bunch of diseases? Would there be some kind of overall pathway shortening also to get these devices more rapidly to market, in addition to just increasing the workload within the FDA?

DR. FOY: This is Joni Foy, acting associate director for policy in the Center for Devices and Radiological Health.

I just wanted to stress that the breakthrough provision that was put in is really an expansion of the expedited access pathway program that CDRH has put into place, which primarily focused on PMA's de novos, which are your higher risk type products. This provision expands the ability for 510(k)s to be explicitly included as part of this provision.

And part of the reason why I guess we were focusing on workload rather than focusing on accelerating innovation, which is truly the ultimate goal in expediting and getting those products into the patients that actually need those products sooner rather than later, was because of the fact that the provision expanded to the 510(k)s.

The other thing was that is one of the things that we are committed to doing as part of this provision and is actually mandated is extensive interaction. We are actually talking about having sprint type of interactions with companies where we are meeting with them and having dialogue and discussion with them from the inception of their product all the way through the total product lifecycle. And when I say sprints, I am talking about meeting with them on a biweekly or weekly type of fashion where we are engaging in real-time dialogue, so we can work through issues in a more expeditious and efficient manner, both for the agency as well as for the stakeholder, who is trying to develop that product.

So that is why we are mentioning here the fact that this is a resource-intensive program.

DR. SARWAL: Right. Thank you so much.

DR. McLELLAN: Any further comments?

Hearing none, let's go to Section 3052, humanitarian device exemption. Basically, the guidance here is looking for FDA to establish guidance that defines the criteria for establishing probable benefits when you are involved with marketing a humanitarian device with an exemption.

Are there comments on this section?

DR. TOSI: Hi, this is Laura Tosi. I am not sure if this fits here. Again, a little bit of a personal experience problem.

The FDA very appropriately tightened up its humanitarian device rules about 5 years ago, unfortunately, because primarily orthopedic surgeons had really misbehaved and tried to avoid other FDA rules for experimenting with new implants. And that was very appropriate, but what got lost in the shuffle was that sometimes when you are dealing with a very rare disease, you need a one-off and you need it like in the next 24-48 hours.

We are supposed to be happy because, well, you will get your approval in 30 to 60 days. Well, a patient can be dead if they are lying around not getting what they need.

I think a better look at the humanitarian device exemption needs to be taken because it really is

working against patients right now.

DR. McLELLAN: Laura, your comment fits beautifully with the idea that they need to reissue guidance and look at establishing new criteria.

DR. TOSI: I am very happy to help, because this is where I live, with treating kids with very rare diseases.

DR. FOY: So this is Joni Foy.

Again, I just wanted to actually sort of -- what you are talking about is really the custom device provision.

DR. TOSI: Right.

DR. FOY: It is a separate endeavor that the agency was working on. If you are in a situation where you need immediate access to a product, we have a compassionate use program where you can certainly reach out to the organization. Actually, you need to reach out to the sponsor who essentially manufactures that product. Then we can essentially turn around and typically do within several days a request for approval of that product. There is also an emergency use provision in the event that you cannot actually reach out to the agency in advance of requesting authorization where you can file an emergency use authorization after the fact.

So we do have provisions in place for those situations where you are in an immediate, emergent need for getting access to a product.

The HDE provision, the purpose of the Cures provision is really to expand the ability of the agencies and the companies that are innovating these products to be able to have more access in this space to create innovative products for a larger patient population.

So we see this as a good thing. We are very supportive of this provision. We are trying to work out how this fits into our entire continuum of benefit-risk. So that is really the intent and purpose of this specific provision.

DR. GOLDMAN: This is Lynn Goldman. I kind of read it in a similar way. I am just wondering if this is another place where a little clarification or even a footnote might help, because I think there might be many of us in the clinical world that do not understand the distinctions between all these different programs. I do not know.

DR. FOY: Thank you for that suggestion.

DR. TOSI: Thanks, Lynn. Laura Tosi one more time.

I think what you are not appreciating is

unintended consequences. What happened with the changes that the FDA made a couple years ago was that the legal departments in the device industry went nuts, and they throw roadblocks up that I do not think you folks are even unaware of. So compassionate use just does not make sense, because it is not happening.

DR. FOY: So thank you for your comments.

DR. GOLDMAN: I want to apologize, but I told the FDA staff that I am going to have to get off the phone in about 5 minutes. I just apologize, if you do not hear me, because I have to go to different meeting.

DR. McLELLAN: No worries, Lynn. Thank you.

And thank you for your comments, Laura.

Malcolm, I think this is another place where we might use just a little bit of editing to help understand the separation of humanitarian device versus other pathways.

MR. BERTONI: Duly noted. Thank you, Dr. McCall.

DR. McLELLAN: Laura, your comment regarding compassionate use, I think we could have a conversation on that either one-on-one or otherwise between FDA and yourself. I appreciate that input though, and I am quite sure they are appreciative of those thoughts also.

DR. TOSI: Thank you.

DR. McLELLAN: Let's go ahead and move on to Section 3053, recognition of standards, basically calling for FDA to expand their awareness, engagement, and participation in international and national standard settings.

Are there comments regarding this section of the plan?

Hearing none, let's go forward to 3056, International Review Board flexibility. This actually is where my comments previously would have been better applied. That is the encouragement of the use of centralized RIBs, and all I was commenting on prior to is be careful what you ask for. Centralized RIB reactions can be very interesting, in that often they will want to redistribute risk by re-engaging distributed RIBs. It is an interesting world we are watching as this involves.

Other comments regarding Section 3056?

Then I will let my comments stand, and we will move on to Section 3058, looking at least burdensome device review. I will not even comment on this. I will let this stand.

Are the comments from the committee regarding this section?

DR. JENKINS: Annalisa Jenkins.

DR. McLELLAN: Go ahead, Annalisa.

DR. JENKINS: Just with a comment applied probably to Sections 3053 all the way through 3060.

For the future, it might be useful to provide a little bit more clarity about the timeliness of implementation. I applaud all of these, actually, these recommendations in this plan. I think they are timely, appropriate, and applying in this case specifically to the rapid advance in innovation in this space. It just might be useful in the plan just to give some timeliness to when you believe that you can start to implement this and have it fully implemented, because I think that might be quite useful for the relevant manufacturers and stakeholders in this space.

DR. McLELLAN: Very good. Thank you, Annalisa.

Other comments?

Hearing none, let's move to Section 3060 clarifying medical device software. It specifically calls for an extension exemption of categories of medical devices where you have low levels of risk to patients.

Are there comments from the committee regarding this section?

Hearing none, let's go ahead and move forward to Subtitle G focusing on expertise and outreach.

Section 3073 focuses on the intercenter institutes, asking FDA to establish one or more intra- or inter-center institutes to help in the development of various devices and programs.

So are there comments from the committee regarding this section?

DR. STEELE: This is Scott Steele with a question.

DR. McLELLAN: Go ahead, Scott.

DR. STEELE: Thank you. I was curious, as an intercenter institute, where FDA envisioned them sitting within the agency. I guess since they said already the Oncology Center of Excellence, where that sits currently.

DR. McLELLAN: Comments from the FDA?

DR. KIM: This is Tamy Kim, Oncology Center of Excellence. The Oncology Center of Excellence has been established within the Office of the Commissioner under the Office of Medical Products and Tobacco.

DR. McLELLAN: So it sits at the commission itself?

DR. KIM: Right.

DR. McLELLAN: Very good. Thank you.

Other comments regarding this section?

DR. JENKINS: Annalisa Jenkins again.

I just, again, for the record, the Oncology Center

of Excellence initiative, it is unofficial and now official, just in my view has been such a remarkably progressive and impactful initiative for the agency and was clearly documented with positive results. I would just hope and encourage the agency to explore a second to be defined.

I would also hope that the level of investment as it relates to this space could really be accelerated, because I do believe this is an area where there has been tremendous progress on so many levels.

DR. McLELLAN: Very good. Thank you.

We have completed our walk-through. We are now going to move to public hearing. At that point, when we finish public hearing, we will come back to the committee. Given everything we have everything we commented on and what we have heard in the public hearing section, we will then ask you to approve our comments going forward to FDA as an action item that we have already put a motion in place on.

So at this point, let me touch base with Rakesh. I believe I am okay to go ahead and call for our public hearing session?

MR. RAGHUWANSHI: Yes.

DR. McLELLAN: Very good.

So at this point, we will now conduct our open

hearing portion of today's meeting.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making.

Folks, forgive me, I am reading this, because it is a clear statement that we need to make.

To ensure such transparency at the open public hearing section of our board meeting, FDA believes it is important to understand the context of an individual's presentation. So for this reason, FDA encourages you, the open public hearing speaker, at the beginning of your oral statement, to please advise the committee of any financial relationship that you may have with the company or group that may be affected by today's topics in this meeting. If you choose to not address the issue financial relationship at the beginning of your statement, we will not preclude you from your speaking.

As of today, we understand that there is one request to speak. There may be others, and we will query for that.

Right now, we will be hearing from Mr. Jack Mitchell. I will ask that either Jeff Rexrode from FDA assists in recognizing Mr. Mitchell via software or that one of our employees in the public room on campus

assist Mr. Mitchell in unmuting his phone.

Go ahead, Mr. Mitchell. I am allotting you 5 minutes for your presentation.

MR. MITCHELL: Good afternoon. I appreciate the opportunity to address this distinguished panel and our FDA participants. I am mindful that you have been working hard for 2 hours now, and I will try not to take too much of your time.

I am the director of government relations for the National Center for Health Research. We conduct research. We use research data to inform public policy, and we advocate for safe and effective medical products.

NCHR accepts no pharmaceutical or medical device industry money. Therefore, I have no conflicts of interest to present or report.

We strongly support FDA's efforts to strengthen the role of patients, and we urge the agency to define patients as those who use medical products, whether or not they are seriously ill. Certainly, the patient-centric initiatives and patient-oriented series of meetings that Dr. Mullin presented and outlined in her presentation were welcome and certainly very appropriate. I would like to speak to just one additional angle about that.

We know it is a challenge for FDA to attract patients who are truly independent, since so many patient groups are funded by industry and many patients are trained and recruited to participate in FDA meetings by industry. Those industry-supported perspectives are welcome and certainly necessary, if not critical. But we believe you also need to be augmented or hear from independent patient voices.

For example, a recent study by Harvard researchers found that almost all patients that spoke FDA public meetings had ties to the companies that could benefit from their remarks. Another study of the FDA advisory committee meeting on the drug for Duchenne muscular dystrophy reported that of the 51 public speakers, all but one had financial ties to the company that makes the drug. That one public speaker was from our research center.

There are patient organizations that are not funded by industry and can offer a more independent voice. We respectfully suggest that FDA needs to do more to reach out to them and include them.

For example, USA Patient Network is a new national organization consisting of patients who have received training to help them understand clinical trial research, design, and analysis. In that way, they can

serve as confident, low-informed patient representatives on FDA and NIH advisory committees. Our organization also helps vet consumer representatives on FDA advisory panels.

In addition, the Patient, Consumer, and Public Health Coalition is an informal coalition of about two dozen nonprofit patient, consumer, physician, and public health organizations. They work together to prepare public comments for the FDA and other health agencies, and also to educate Congress about important public policy issues. Patients from these organizations have made presentations before FDA advisory panels and public forums. In many cases, they pay their own way to FDA meetings or to provide written comments.

We respectfully ask the Science Board to ensure that FDA enhances efforts in acquiring independent patient voices, not only for new drug development but also in the wide range of public health initiatives in which the agency is engaged.

Your focus today is innovation initiatives mandated by the 21st Century Cures Act. We are concerned that the new law does not guarantee sufficient resources to implement all its mandated FDA provisions.

For example, it encourages the FDA to rely more on preliminary data such as biomarkers and to allow third-party review of devices to replace or supplement FDA's premarket scrutiny. The law has already resulted in the process of FDA deregulating many moderate risk devices that eventually will no longer be required to submit 510(k) applications.

To better ensure safety, FDA needs to expand more resources to improve postmarketing surveillance, particularly of medical devices. Unfortunately, neither the 21st Century Cures nor the FDA user fees that FDA has negotiated provide sufficient resources for effective postmarketing surveillance, particularly for medical devices.

Patients from the USA Patient Network and other independent patient organizations have provided documented evidence to FDA of serious, irreversible harm caused by fast-tracked device approvals and inadequate postmarket surveillance. They tell us that the FDA is sometimes not sufficiently responsive to their requests to strengthen patient safeguards.

In conclusion, we respectfully urge the board to carefully address these patients' recruitment and safety issues as you advise FDA about implementing the 21st Century Cures Act. Engagement perspectives should

include patients who have been harmed by medical products that were not as safe as research indicated, or included risks about which the patients were not adequately warned.

While FDA is appropriately and routinely hearing from patients desperate for new treatments, those are not the only patients who have important perspectives from which the agency can learn.

I thank you very much for your time.

DR. McLELLAN: Mr. Mitchell, thank you for your comments. Your points made regarding independent voices concerning financial ties, these are all well-recognized, and you made an excellent statement there.

I also particularly appreciate your comments regarding other collaborators, including the USA Patient Network, and the concern over the appropriate level of funding for this act.

So thank you very much. I appreciate your comments.

Are there any others online that might be ready to give comments?

MR. RAGHUWANSHI: Mark, this is Rakesh.

DR. McLELLAN: Go ahead.

MR. RAGHUWANSHI: There is no one online who has indicated they would like to make any comments, and

there is nobody else in the public room either, so we can move forward.

DR. McLELLAN: Great. Thanks, Rakesh. I appreciate that.

So we are back in order here. We have a motion on the table to pass on our comments as we have made notes of through our meeting. That motion is ready for a calling to question.

So if we can go ahead and proceed. What I would like to do is ask for a vote in favor of passing our comments on. Just simply say aye right now, committee.

[Chorus of ayes.]

DR. McLELLAN: Are there any nays that would like to hold off on giving comments?

[No response.]

DR. McLELLAN: The ayes have it, and it is unanimous.

So at this point, I think we have conducted and completed our business. I apologize for the rigidity by which I had to run this meeting, committee. But I felt, in order for us to get through and get this done in a reasonable manner, I had to be a little bit more rigid than normal. I appreciate your understanding of that.

With that, I would like to call for a motion to

adjourn. Is there someone who would make that call?

DR. KOWALCYK: Motion to adjourn.

DR. McLELLAN: Thanks, Barb. Appreciate that.

We will take that as a second, and we will move forward to adjournment.

Thank you very much, everyone. We appreciate your time at the committee meeting.

FDA staff, thank you so much for listening to our guidance and comments.

This concludes our meeting. Thank you, everyone, for being a part of our public meeting of the Science Board.

MR. BERTONI: Thank you, Mark. This is Malcolm. I want to thank everyone again. This is very, very helpful. We really appreciate you doing this on such short notice, and with very helpful and thoughtful comments.

DR. McLELLAN: You bet. We appreciate it. Thank you.

[Whereupon, at 4:09 p.m., the meeting was adjourned.]